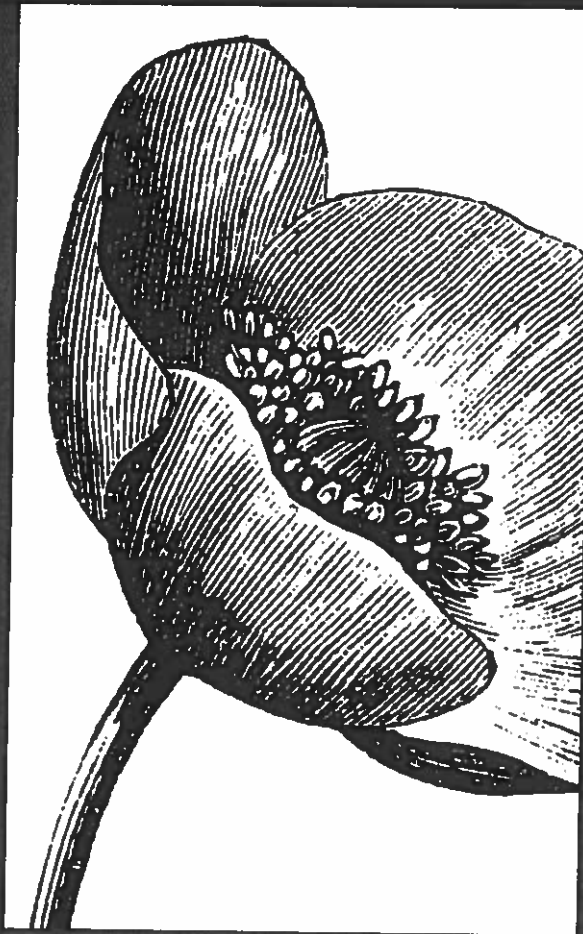


34<sup>TH</sup> ANNUAL MEDICAL SEMINAR ON WORKERS' COMPENSATION

# HISTORICAL PERSPECTIVE ON OPIOIDS

*T. KERN CARLTON, M.D.*

*THE REHAB CENTER*



February 24 – 26, 2013    Francis Marion Hotel, Charleston, SC

## Historical Perspective on Opioids

T. Kern Carlton, M.D.  
Medical Director  
The Rehab Center  
Charlotte, N.C.  
[www.TheRehabCenter.com](http://www.TheRehabCenter.com)

---

---

---

---

---

---

---

---

## Early History

Opium poppies in bloom



- The ancient Sumerians, inhabiting present-day Iraq, were known to cultivate opium poppies and produced opium from them as early as around 4000 BC. They called it "gil," the word for joy.
- Opium then spread from there throughout the ancient world.

---

---

---

---

---

---

---

---

## Early History



Opium was initially used as a euphoriant in religious rituals, and then came to be used along with hemlock to put people quickly and painlessly to death.

Opium came to be used medicinally thereafter. The *Ebers Papyrus* from ca. 1500 BC describes the use of opium as a remedy "to prevent excessive crying of children."

---

---

---

---

---

---

---

---

**Ancient Greece and Rome**

- The ancient Greeks and Romans ingested opium for both medical treatment and recreational purposes.
- In Greece around 460 BC, Hippocrates and Galen were both known to have employed opium to treat everything from headaches and coughing through asthma and melancholy.

---

---

---

---

---

---

---

---

**The "Downside": Side Effects**

- Constipation
- Nausea/vomiting
- Sexual impairment/androgen deficiency
- Cognitive impairment
- Potential for addiction, dependence, tolerance, and abuse
- Most dangerous: Acute respiratory depression potentially resulting in death

---

---

---

---

---

---

---

---

**Withdrawal Symptoms**

- Anxiety
- Insomnia
- Vomiting
- Irritability
- Salivation
- Nausea
- Lacrimation
- Rhinorrhea
- Diaphoresis
- Abdominal Cramps

---

---

---

---

---

---

---

---

### Middle Age(s) Spread

- Arab traders brought opium to India and China as early as the 8<sup>th</sup> century, and between the 10<sup>th</sup> and 13<sup>th</sup> centuries opium made its way from Asia Minor to all parts of Europe.
- Starting in the 16<sup>th</sup> century, manuscripts in Turkey, Egypt, Germany, and England describe problems with drug abuse and tolerance.
- The problem of addiction becomes especially severe in China in the mid-17<sup>th</sup> century, after tobacco smoking was banned.

---

---

---

---

---

---

---

---

### The Emergence of Morphine

- In 1804, Sertürmer isolated the active ingredient in opium and named it morphine, after the Greek god of dreams, Morpheus. It was first marketed in 1817 for analgesia and as a "cure" for opium and alcohol addiction.
- After the invention of the hypodermic syringe and hollow needle in the 1850's, morphine began to be used for minor surgical procedures, and for postoperative and chronic pain.

---

---

---

---

---

---

---

---

### Opiates in the U.S.

- Morphine was used extensively during the American Civil War, allegedly resulting in 400,000 cases of what was called the "soldier's disease" – morphine addiction.
- In 1898, heroin was synthesized and first marketed as a cough suppressant. It was initially claimed to be non-addictive, and in the early 1900's free samples were distributed to recovering morphine addicts as a "step-down" cure.

---

---

---

---

---

---

---

---

### The U.S. Federal Government Intervenes

- In 1909, the the Smoking Opium Exclusion Act was passed banning the importation, possession, and use of "smoking opium" (but not opium-based medications), the first Federal law banning the non-medical use of a substance.
- In 1924, recognizing its addictive and dangerous qualities, the Heroin Act was passed, making the manufacture, importation, and possession of heroin illegal, even for medicinal use.

---

---

---

---

---

---

---

---

### Recent History of Opioids in American Medicine

- In the mid 1980s, the World Health Organization began encouraging doctors to use opioids to treat cancer patients for pain.
- In 1995, national medical advocacy groups, many of which were funded by pharmaceutical companies, began advising doctors to use the drugs for non-cancer pain as well.
- In 2001, the JCAHO codified this recommendation and required doctors to treat pain as a disease rather than as a symptom of another condition. In addition, the government approved use of opioids for "moderate to severe pain," vastly broadening the potential market.

---

---

---

---

---

---

---

---

### The Threat of "Undertreatment"

- In a landmark case in 2001, a California jury awarded a \$1.5 million verdict against a physician for reportedly failing to treat a cancer patient's pain adequately and thereby causing him needless suffering.
- Somehow, concerns about the potential undertreatment of pain in patients with cancer were generalized to patients with chronic non-malignant pain, for whom there is no clear endpoint of cure or death.

---

---

---

---

---

---

---

---



---

---

---

---

---

---

---

---

### Non-Malignant Pain

- Not due to cancer
- Not life threatening
- Often poorly localized
- Often not well defined by specific pathology
- 20 to 40% of adults in the U.S. report chronic non-cancer pain

---

---

---

---

---

---

---

---

### The Push To Prescribe Opioids

- The practice of using opioids for chronic pain treatment was strongly reinforced by continuing medical education classes and state regulations encouraging physicians to treat pain "appropriately," with immunity from prosecution for potential overprescribing.
- At the same time, the drug companies began aggressively marketing opioids— particularly stronger, long-acting formulations — as safe at any dosage and less addictive. One such company (Purdue Pharma) came to a \$160 million settlement with the Federal government in 2007 on allegations that it misrepresented the dangers of its product, OxyContin.

---

---

---

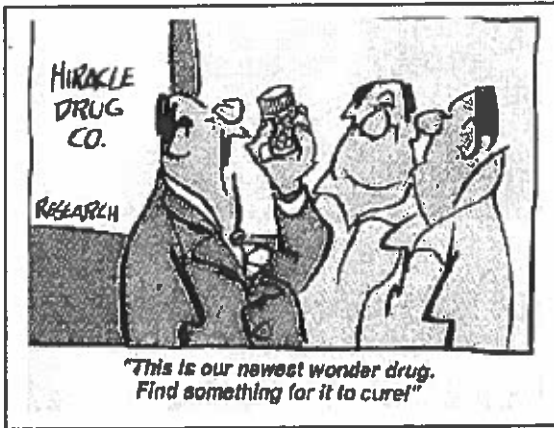
---

---

---

---

---



---

---

---

---

---

---

---

---

**The United States Senate Finance Committee Investigation**

- An investigation was launched by the Senate Finance Committee in May 2012, looking into the marketing practices of pharmaceutical and medical device companies as well as their relationships with physicians and non-profit medical organizations.
- The Committee stated that "it is clear that the United States is suffering from an epidemic of accidental deaths and addiction resulting from the increased sale of powerful narcotic painkillers."
- It went on to note increasing evidence that "pharmaceutical companies that manufacture and market opioids may be responsible, at least in part, for this epidemic by promoting misleading information about the drugs' safety and effectiveness."

---

---

---

---

---

---

---

---

**"A Body of Dubious Information"**

- The Committee quoted the finding that a "network of national organizations and researchers with financial connections to the makers of narcotic painkillers... helped create a body of dubious information" favoring opioids "that can be found in prescribing guidelines, patient literature, position statements, books and doctor education courses."
- The investigation remains underway.

---

---

---

---

---

---

---

---

### Opioids In The U. S. Today

- As of 2010, Americans made up 4.6% of the world's population, but used 80% of the world's opioid supply, 99% of the world's hydrocodone supply, and two-thirds of the world's illegal drugs.
- Opioids have become the most commonly prescribed drug category in the U.S. Fifteen to 20% of office visits in the U.S. now include the prescription of an opioid.
- By 2010, enough opioid prescriptions were sold to medicate every American adult with a typical dose of 5 mgs of hydrocodone every four hours for one month.
- Opioids are the most common treatment for chronic pain--as many as 90% of pain management patients in the U.S. receive opioids for chronic pain.

---

---

---

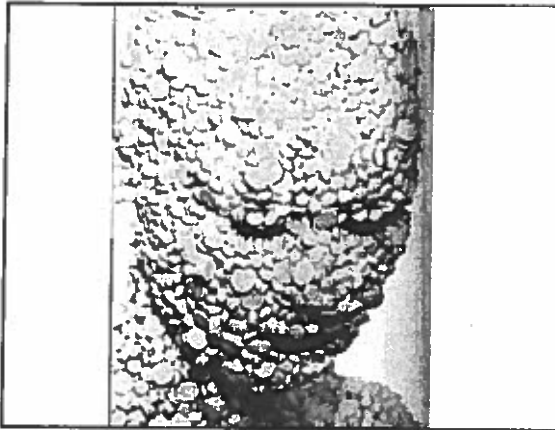
---

---

---

---

---



---

---

---

---

---

---

---

---

### Prescription Patterns

- Most prescription opioids are prescribed by primary care and internal medicine doctors and dentists, not specialists.
- Roughly 20% of prescribers prescribe 80% of all prescription painkillers.
- Unfortunately, a number of physicians, medical aides and pharmacists prescriptions have contributed to the illegal prescription drug epidemic. At least 30 have been indicted since 2010 for illegally prescribing opioids, and many more have been disciplined.

---

---

---

---

---

---

---

---



### A Public Health Menace

- As prescriptions for opioids have increased exponentially, there have been parallel increases in the use of these as recreational drugs, with corresponding increases in the number of overdoses and deaths, as well as individuals seeking treatment for substance abuse.
- In 2011, half of arrests for DWI involved not alcohol, but opioids.
- Opioids have become the most popular recreational drug among adolescents, surpassing marijuana, cocaine, and others.

---

---

---

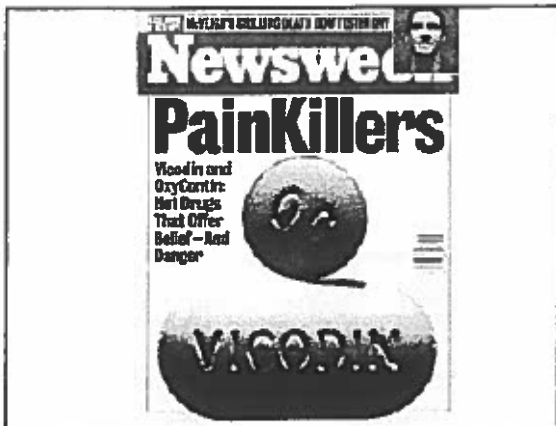
---

---

---

---

---



---

---

---

---

---

---

---

---

### A Public Safety Menace

- The number of U.S. drugstore robberies rose 80 percent between 2006 and 2011.
- On Long Island, New York, a pharmacist, cashier and two customers were murdered in broad daylight in June 2011 by David Laffer, an addicted gunman stealing more than 10,000 hydrocodone pills.

---

---

---

---

---

---

---

---

### New York City's Response

- The NYC Office of the Special Narcotics Prosecutor, formed in 1971 in response to the city's heroin epidemic, has now created a special Prescription Drug Investigation Unit.
- The Special Narcotics Prosecutor has been pushing for stronger laws against the "pill mill" doctors and pharmacists who knowingly prescribe opioids to clearly addicted people, stating that they "ought to be punished like any other drug dealer."

---

---

---

---

---

---

---

---

### Physician Charged With Manslaughter

- The pain management physician who was accused of supplying drugs to David Laffer was indicted in December 2012 on manslaughter (among other charges) in connection with the deaths by overdose in 2009 and 2010 of two men for whom he had prescribed lethal amounts of highly addictive prescription medications, including oxycodone and Xanax.

---

---

---

---

---

---

---

---

### Opioid Overdose Deaths in the U.S.

- As of 2008, there were 14,800 annual deaths by opioid overdose in the U.S, up from 4,000 opioid overdose deaths in 1999. It is estimated that that number at present is around 16,500 people.
- The number of overdoses has increased significantly every year, in tandem with increased prescriptions of opiates.

---

---

---

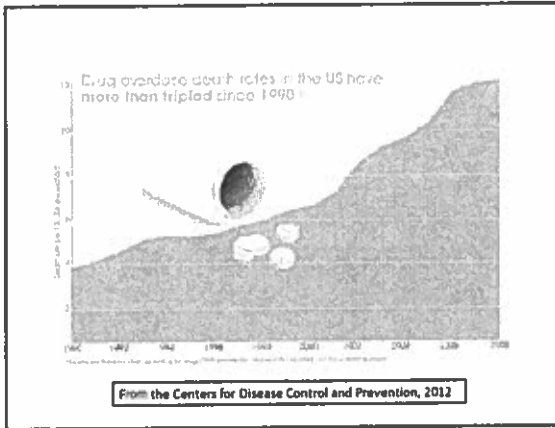
---

---

---

---

---



---

---

---

---

---

---

---

---

### Long-acting Opioids Increase the Risk of Overdoses and Deaths

- An epidemiological study in the Canadian province of Ontario found that the addition of long-acting oxycodone (OxyContin) to the drug formulary was associated with a 5-fold increase in oxycodone-related mortality and a 41% increase in overall opioid-related mortality.

---

---

---

---

---

---

---

---

### Nonfatal Opioid Overdoses

- One study of 9940 patients found roughly seven nonfatal overdoses for each fatality.
- Nearly half a million emergency department visits in 2009 were due to people misusing or abusing prescription opioids.
- Nonmedical use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs.

---

---

---

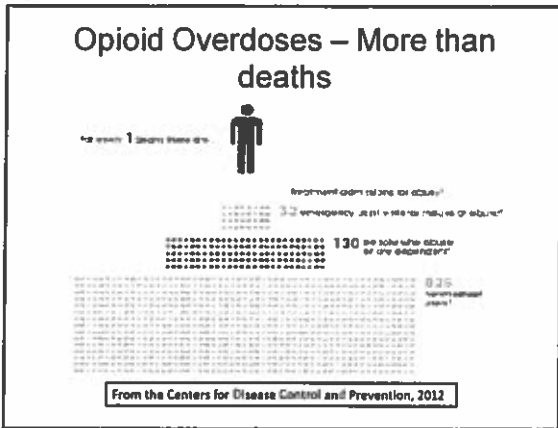
---

---

---

---

---



---

---

---

---

---

---

---

---

- ### Populations at Greatest Risk for Opioid Abuse or Overdose
- Men, much more so than women
  - Middle-aged adults
  - Smokers
  - Low-income people and those living in rural areas.
  - People with a history of treatment for depression or mental illness and those with a history of substance abuse.
  - People who take long-acting opioids, high dosages of opioids and those who concurrently use alcohol and/or benzodiazepines.
  - "Doctor shoppers"/patients using multiple providers
- From the Centers for Disease Control and Prevention, 2012

---

---

---

---

---

---

---

---



---

---

---

---

---

---

---

---

### Potential Medical Complications of Long-Term Opioid Use

Long-term opioid use, inadequately studied to date, entails many potential medical risks in addition to overdose and addiction, including:

- falls and fractures
- chronic constipation and serious intestinal blockage
- breathing difficulties during sleep
- hormonal and endocrine dysregulation (potentially contributing to sexual dysfunction, osteoporosis, and depression)
- immunosuppressive effects that may contribute to infection risk
- cardiovascular disease risks
- increased risks of motor vehicle accidents; and
- risks of cognitive and neuropsychologic impairments such as sedation, delirium and dementia
- Depression, anxiety, apathy

---

---

---

---

---

---

---

---

---

---

### The PROP Petition

The Physicians for Responsible Opioid Prescribing (PROP), comprising clinicians, researchers, and health officials from multiple fields in medicine, summarized a number of concerning findings regarding the long-term prescription of opioids to patients with chronic non-cancer pain (CNCP). These were sent in a Citizen Petition to the FDA on July 26, 2012, along with the following proposals:

---

---

---

---

---

---

---

---

---

---

### The PROP Petition

SPECIFIC ACTIONS REQUESTED FOR CHANGES TO OPIOID ANALGESIC LABELS:

1. Strike the term "moderate" from the indication for non-cancer pain.
1. Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain.
2. Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain.

---

---

---

---

---

---

---

---

---

---

### Pushback

- Given the sums of money at risk and the careers at stake, it is unsurprising that the pharmaceutical industry and several groups funded in part by them have objected to the PROP Petition.
- Shortly after the PROP Petition was filed, the American Academy of Pain Medicine (AAPM; one of the non-profit organizations under investigation by the Senate Finance Committee) called the PROP proposals "seriously flawed, potentially harmful to patients with debilitating pain conditions for whom opioid therapy is indicated, and without substantive scientific foundation."

---

---

---

---

---

---

---

---

### PROMPT Response

- A group of 26 physicians and pharmacists called Professionals for Rational Opioid Monitoring and Pharmacotherapy (PROMPT) endorsed the AAPM response and sent a letter to the FDA suggesting an alternative approach-- emphasizing "clinical education, proactive risk stratification, and appropriate therapeutic monitoring."
- They have suggested a variant of the FDA's recently-released risk management plan for long-acting opioids, with mandated physician training

---

---

---

---

---

---

---

---

### PROMPT Response

- PROMPT has opposed the limitations on opioid therapy proposed by PROP, and has instead argued for making education mandatory for all clinicians who prescribe opioids.
- They note that methadone accounts for 2% of all opioid prescriptions, but 33% of overdose deaths, attributing this to improper patient selection and education by insufficiently-trained clinicians.

---

---

---

---

---

---

---

---

### Dr. Portenoy recants

- Dr. Russell Portenoy, one of the leading champions of more liberal opioid prescribing for chronic pain, stated in an interview with the *Wall Street Journal* on December 17, 2012, that in hindsight "it was the wrong thing to do."
- Dr. Portenoy acknowledged greatly underreporting the addiction potential of opioids.
- Dr. Portenoy admitted that "data about the effectiveness of opioids (for the chronic pain population) does not exist."

---

---

---

---

---

---

---

---

### What is the existing evidence?

As just mentioned, Dr. Portenoy acknowledged the lack of scientific evidence of the effectiveness of opioids for chronic non-cancer pain.

In fact, the physicians drafting the PROP petition noted the following important findings:

- Recent surveys show that many patients with chronic pain receiving long-term opioids continue to experience significant chronic pain and dysfunction.
- A large sample of medical and pharmacy claims records found that 2/3 of patients who took opioids on a daily basis for 90 days were still taking opioids five years later.

---

---

---

---

---

---

---

---

### Do Opioids *Interfere* with Recovery From Chronic Pain?

- A 2010 population-based study in Denmark, found that over a six-year period, 52.1% of patients diagnosed with chronic pain were largely pain-free at six-year follow-up. However, patients treated with opioids were *four* times more likely *not* to recover during that time period.
- Similarly, Rainville and others have noted that patients on opioids report decreased functional improvements in rehabilitation than otherwise similar patients not using opioids.

---

---

---

---

---

---

---

---

### Poorer Outcomes for Workers Compensation Patients

- A 2009 study concluded that individuals on high-dose opioid therapy after work-related injuries had poorer outcomes— in terms of return-to-work, work retention, medical utilization, and long-term disability status— than those who did not opt for opioids.
- Workers who receive high doses of opioids to treat injuries such as back sprains stayed out of work *three times longer* than those with similar injuries who took lower doses, according to a 2008 study.

---

---

---

---

---

---

---

---




---

---

---

---

---

---

---

---

### Evidence Regarding the Safety of Opioids

There are many reports regarding the risks of addiction, overdoses, and further injuries sustained by patients on long-term opioid therapy.

- Recent surveys using DSM criteria found high rates of addiction in CNCP patients receiving chronic opioid therapy.
- Three large observational studies published in 2010 and 2011 found dose-related overdose risk in CNCP patients on chronic opioid therapy.
- COT at high doses is associated with increased risk of overdose death, emergency room visits and fractures in the elderly.

---

---

---

---

---

---

---

---



### Changes in the FDA's Stance

- On January 25, 2013, an advisory panel of experts to the FDA voted to toughen restrictions on hydrocodone so as to require written prescriptions by physicians, disallowing those called in by phone or fax, refills without a written prescription, or prescriptions by NP's or PA's.
- The FDA denied a similar request by the DEA in 2008. However, the DEA requested that the FDA reconsider its position in light of new data, leading to the convening of this panel.

---

---

---

---

---

---

---

---

### Present Status

- The FDA is thought likely to follow this recommendation, which would then be sent to officials at the Department of Health and Human Services, who will make the final determination.
- The FDA is expected to rule on the proposed changes in the PROP proposal in February 2013.

---

---

---

---

---

---

---

---



---

---

---

---

---

---

---

---