#### OPIATES and MEDICINE WHERE ARE WE, AMERICA?



## **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

Jeffrey Berger M.D.

FASAM, Board Certified in Addiction Medicine Medical Director, Brighton Center for Recovery Unabashed supporter of Abstinence-Based, 12 Step Recovery

Otherwise: Nothing to declare!



#### **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

## OBJECTIVE 1: LEARN THE HISTORY OF OPIATES IN MEDICINE

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Malia remanchior		
PHILADELPHIA: LINDSAY AND BLAKISTON. 1846.		

# OPIATES and MEDICINE

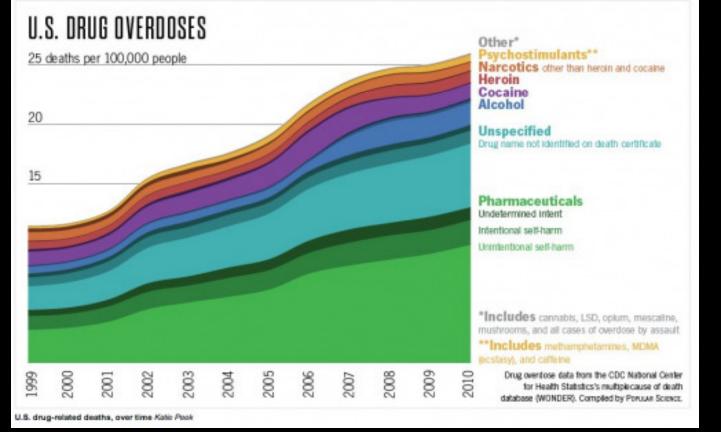
- OBJECTIVE 2:
- UNDERSTAND OPIATE ADDICTION AS A BRAIN DISEASE



WHERE ARE WE, AMERICA?

#### **OBJECTIVE 3:**

## **ISSUES IN THE USE OF OPIATES TO TREAT CHRONIC PAIN**



## **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

- OBJECTIVE 4
- DISCUSS THE MEDICAL TREATMENT OF ADDICTION

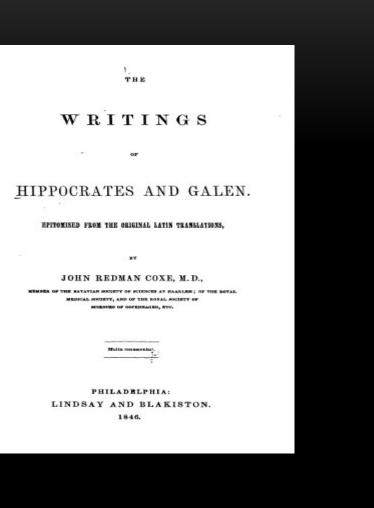






#### **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

## OBJECTIVE 1: LEARN THE HISTORY OF OPIATES IN MEDICINE





- It all starts here with the most well known poppy – Papaver Somniferum
- (One translation of the Latin would be "Sleep-manufacturing Poppy")









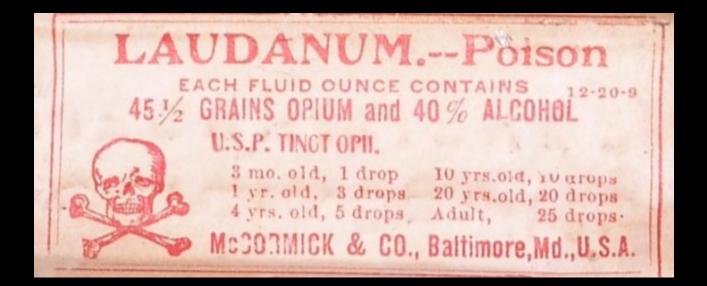
- The word "Opium" comes from the Greek word for "sap" (Opion).
- Prior to the "Scientific Revolution" of the 1800's, Opium itself was the only available Opiate.

- **Opium** was used to treat a variety of conditions:
  - Headache
  - Pain (including surgical pain)
  - Diarrhea
  - Insomnia
- **Opium** could be taken orally or smoked (often combined with tobacco after the discovery of the New World).

## **OPIATES** and **MEDICINE**

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After the 1500s, commonly administered as LAUDANUM (tincture of opium – which is opium dissolved in alcohol).



## OPIATES and MEDICINE WHERE ARE WE, AMERICA?

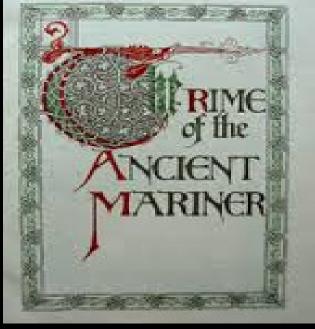
#### FAMOUS OPIUM Addicts



## **OPIATES** and **MEDICINE**

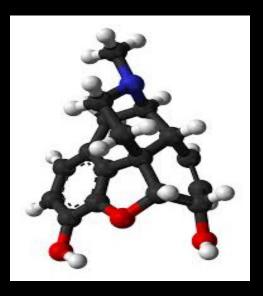
#### FAMOUS OPIUM ADDICTS



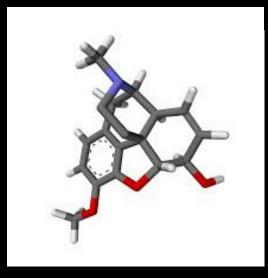


WHERE ARE WE, AMERICA?

- Opium itself, however, is a mixture of many (at least 50) different alkaloids. Only two of these alkaloids are analgesic in humans. They are:
  - Morphine

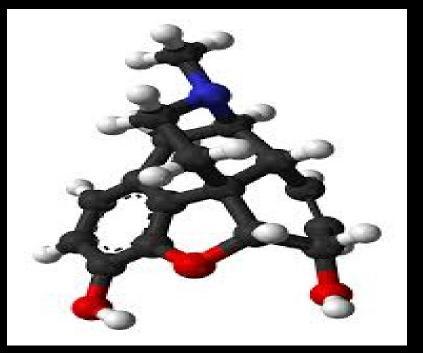


#### Codeine



WHERE ARE WE, AMERICA?

# Morphine



## OPIATES AND MEDICINE where are we, America? MORPHINE 1804/1827



In nature, Morphine comes only from Papaver Somniferum.

There are different varieties of this poppy (called "cultivars"). Some produce as little as 0.04% Morphine; others can contain as much as 26% Morphine (by weight).



#### OPIATES AND MEDICINE WHERE ARE WE, AMERICA? MORPHINE

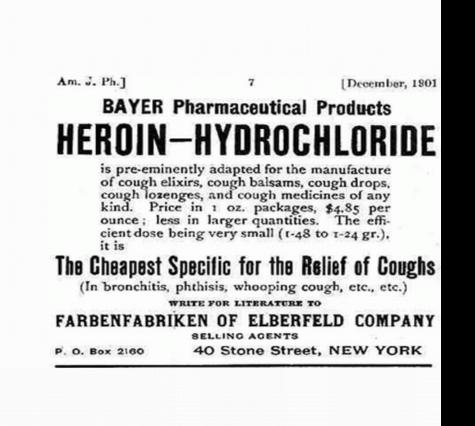
- Morphine was named after the Greek God of Dreams –
   Morpheus.
- Throughout the 1800's and into the 20<sup>th</sup> Century, chemists attempted to "improve" Morphine.
   By the 1920, 2 different drugs, each possessing narcotic effects were developed:
  - Diacetyl morphine
  - Hydromorphone

# OPIATES and MEDICINE where are we, America?

#### DIACETYL MORPHINE 1874/1898

• First of the "semi-synthetic" opiates





## OPIATES AND MEDICINE WHERE ARE WE, AMERICA? HEROIN

- Harrison Narcotics Tax Act, 1914
- Public Acts of the Sixty-Third Congress of the United States
- Woodrow Wilson, President; Thomas R. Marshall, Vice-President; James P. Clarke, President of the Senate pro tempore; Claude A. Swanson, Acting
  President of the Senate pro tempore, December 21 to 23, 29 to 31, 1914, and January 2, 1915; Nathan P. Bryan, Acting President of the Senate pro
  tempore, January 22, 1915; Champ Clark, Speaker of the House of Representatives
- Chap 1. An Act To provide for the registration of, with collectors of internal revenue, and to impose a special tax on all persons who produce, import, manufacture, compound, deal in, dispense, sell, distribute, or give away opium or coca leaves, their salts, derivatives, or preparations, and for other purposes.
- Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, that on and after the first day of March, nineteen hundred and fifteen, every person who produces, imports, manufactures, compounds, deals in, dispenses, distributes, or gives away opium or coca leaves or any compound, manufacture, salt, derivative, or preparation thereof, shall register with the collector of internal revenue of the district, his name or style, place of business, and place or places where such business is to be carried on: Provided, that the office, or if none, then the residence of any person shall be considered for purposes of this Act to be his place of business. At the time of such registry and on or before the first of July annually thereafter, every person who produces, imports, manufactures, compounds, deals in, dispenses, distributes, or gives away any of the aforesaid drugs shall pay to the said collector a special tax at the rate of \$1 per annum: Provided, that no employee of any person who produces, imports, manufactures, or gives away any of the aforesaid drugs, acting within the scope of his employment, shall be required to register or to pay the special tax provided by this section: Provided further, That officers of the United States Government who are lawfully engaged in making purchases of the above-named drugs for the various departments of the Army and Navy, the Public Health Service, and for Government hospitals and prisons, and officers of State governments or any municipality therein, who are lawfully engaged in making purchases of the above-named drugs for State, county, or municipal hospitals or prisons, and officials of any Territory or insular possession, or the District of Columbia or of the United States who are lawfully engaged in making purchases of the above-named drugs for hospitals or prisons therein shall not be required to register and pay the special tax as herein required.
- It shall be unlawful for any person required to register under the terms of this Act to produce, import, manufacture, compound, deal in, dispense, sell, distribute, any of the aforesaid drugs without having registered and paid the special tax provided for in this section.

## **OPIATES** and **MEDICINE** where are we, AMERICA?

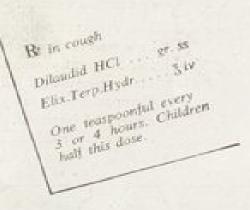
## HYDROMORPHONE 1924/1926

#### APPROXIMATE COMPARATIVE ANTITUSSIVE AND ANALGESIC DOSES OF OPIATES

- To control cough 1/64 gr. Dilaudid is equivalent to 1/4 gr. codeine.
- For analgesia 1/20 gr. Dilaudid will usually replace 1/4 gr. morphine or 1 gr. codeine. Dilaudid is given for pain relief, not for hypnosis.
- Dilaudid may be habit forming, and requires a narcotic prescription.

Dilaudid hydrochloride is available in various strength hypodermic tablets, in ampules, oral tablets and powder.

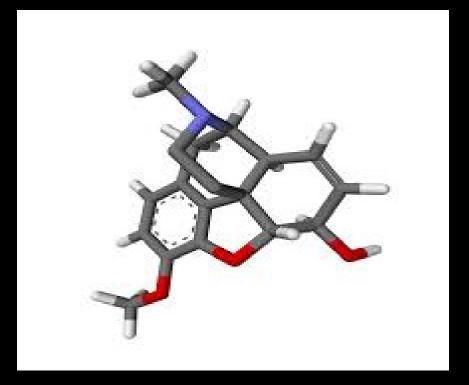
Dilandidm, brand of Dibydromorphinons, a product of F. Billinder, Im-



Dilaudid BILHUBER-KNOLL CORP. distributor ORANGE, NEW JERSEY

WHERE ARE WE, AMERICA?

# Codeine



# OPIATES AND MEDICINE where are we, America?

 Codeine (poppy head) is also found naturally in opium. It was first isolated in 1832, is still available over the counter in Canada - "222 tablets."



• Codeine also was "improved." HYCODAN, first synthesized in 1920, was marketed in the US in 1943.

WHERE ARE WE, AMERICA?

• Papaver Bracteatum



#### Papaver Somniferum



WHERE ARE WE, AMERICA?



**Thebaine,** although occurring naturally, has no use in medicine. It has no analgesic effects, produces seizures.

It is, however widely used by the pharmaceutical industry to produce a variety of opiates for medicinal use.

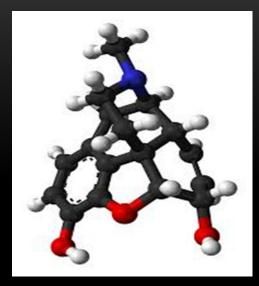
WHERE ARE WE, AMERICA?

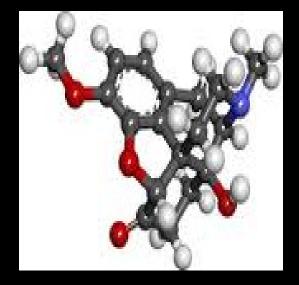
#### • Morphine

- Hydromorphone
- Diacetyllmorphine (Heroin)
- Codeine
  - Hydrocodone

#### • Thebaine

- Group 1
  - Oxycodone
  - Oxymorphone
- Group 2
  - Nalbuphine
  - Buprenorphine
- Group 3
  - Naloxone
  - Naltrexone





## **OPIATES and MEDICINE**

WHERE ARE WE, AMERICA?

A NOTE ON URINE DRUG SCREEN TESTING

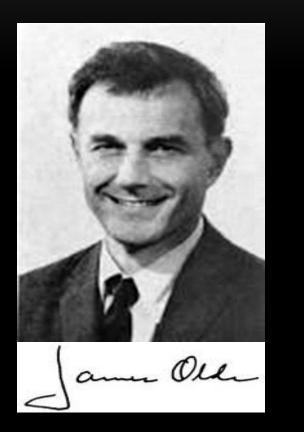
## • TYPICAL URINE DRUG TEST FOR OPIATES:

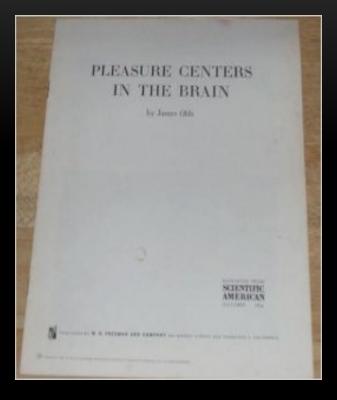
- RELIABLY TESTS FOR MORPHINE AND CODEINE
- MOST TESTS WILL ALSO SHOW IF HYDROCODONE (Vicodin, Norco, Lortab and others) IS PRESENT.
- ALMOST ANY OTHER OPIATE WILL NEED SPECIAL TESTING, BUT CHECK WITH YOUR LABORATORY TO SEE WHICH OPIATES THEIR TESTS DETECT.

## **OBJECTIVE 2**

## OPIATE ADDICTION AS A BRAIN DISEASE OPIATES AND MEDICINE WHERE ARE WE, AMERICA?

## **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?





"Where then dwell the 'higher feelings,' such as love, fear, pain and pleasure?..."

## **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

The goal of Dr. Olds' research was to see if he could locate areas of the brain where "stimulation might be sought rather than avoided by the animal."



James Olds, Pleasure Centers in the Brain; Scientific American: 1956, pp 105-116

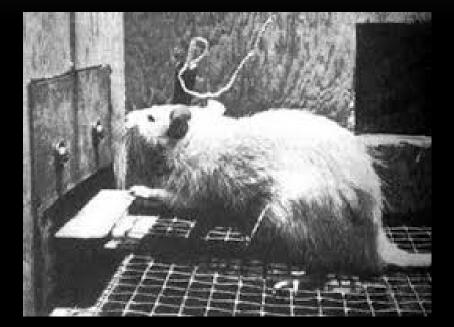


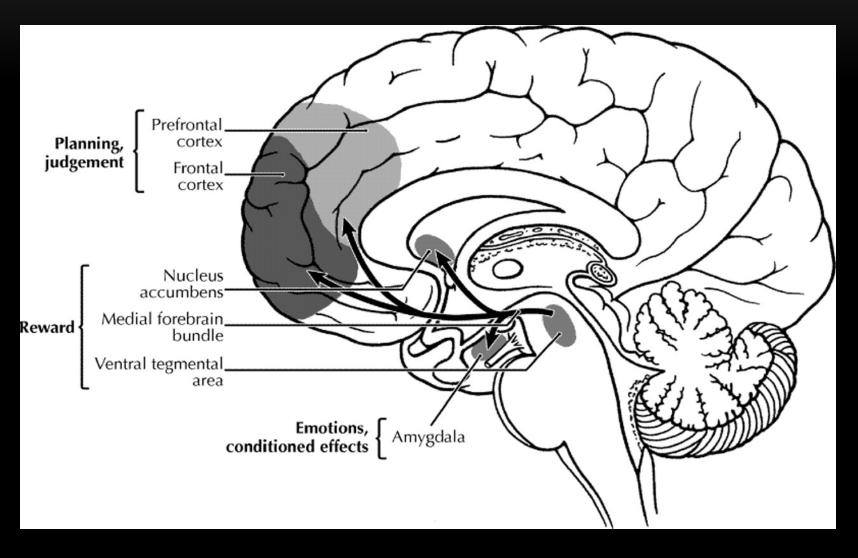
## **OPIATES** AND **MEDICINE** WHERE ARE WE, AMERICA?

## ADDICTION

• Depending on which part of the brain was stimulated, the rat would press the pedal anywhere from 200 times per hour (over three times per minute) up to 5,000 times per hour (over 80 times per minute or more than once every second).

ADDICTION



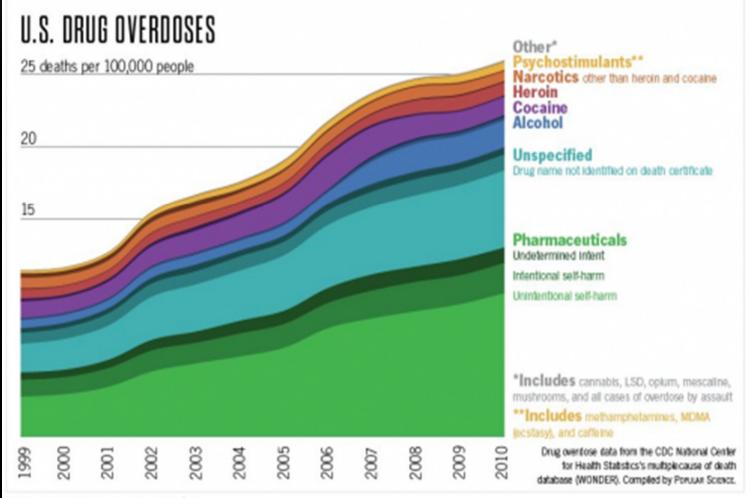


**OBJECTIVE 3** 

# DISCUSS ISSUES IN THE USE OF OPIATES TO TREAT CHRONIC PAIN OPIATES AND MEDICINE

### **OPIATES and MEDICINE**

#### WHERE ARE WE, AMERICA?



U.S. drug-related deaths, over time Katic Pock

### PRESCRIPTION DRUG EPIDEMIC – HOW DID WE GET THIS WAY?

**OPIATES** and **MEDICINE** Where are we, America? In 1986, Dr. Steven Portenoy coauthored an article about treating chronic, non-malignant pain. (Portenoy RK, Foley KM. Chronic use of opioid analgesics in nonmalignant pain: report of 38 cases. Pain 1986; 25:171-86.)

#### PRESCRIPTION DRUG EPIDEMIC – HOW DID WE GET THIS WAY?

#### **OPIATES** and **MEDICINE** Where are we, America?

Dr. Portenoy based his work on a one paragraph "study" in the NEJM that he believed to be true – that said that less than 1% of patients treated for ACUTE pain (during a hospital visit) would become addicted. (Porter J, Jick H. Addiction rate in patients treated with narcotics. New England Journal of Medicine 1980; 302:123.)

His own research consisted of a report of 38 patients, which he used as proof of the validity of the 1% figure.

> IS A VITAL SIGN

# 0.6 OxyContin (oxycodone HCl controlled-release) neperidine HCl ard water on "The New Oxy Contin"

# SUBLIMAZE **COUPON**

#### Pharmacy Instructions

Submit a primary claim using the following pharmacy processing information. For processing questions and comments please call the Pharmacy Helpline below.



THIS IS NOT INSURANCE

Customer Service: 800-726-4232 Pharmacy Helpline: 877-321-6755





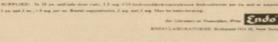


### **OPIATES** AND **MEDICINE** where are we, America?

#### One of the most significant advances in analgesics since the isolation of morphine in 1805

An analgesic capable of replacing morphine and morphine-like synthetic agents in a very wide range of clinical applications

NUMORPHAN<sup>++</sup> provides: unexcelled pain relief jeffective in much smaller doses than morphine (L/10 the morphise dosage) jrapid onest of action -10-26 minutes after administration j prolonged duration of effect. Lasts about 6 hours /low incidence of side affects, respiratory depression, missis, and constipution are relatively rare genut tope of pain relief in shortand long-term therapy ino "plateau effect": in ultrasevere pain, increasing the dose will usually ensure thereapy ino "plateau effect" in ultrasevere pain, increasing the dose will usually ensure thereapy ino "plateau effect".







#### Oxymorphone:

- Developed 1914
- Marketed in US in 1959
- Withdrawn from market in 1972

#### Oxymorphone:

- Developed 1914
- Marketed again in 2006
- Reformulated 2013

🖉 A Pain-Drug Champion Has Second Thoughts - WSJ.com - Windows Internet Explorer	
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WSJ / WHAT DOES A DOLLAR GET YOU TODAY? ONLY \$1 AWEEK FOR 12 WEEKS . SUBSCRIBE NOW » For a limited time	For business, for family, for life.
By THOMAS CATAN and EVAN PEREZ	
Updated Dec. 17, 2012 11:36 a.m. ET	
	en it's a NetJets flight, whatever you need it to be.
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- Points from the article:
- 1. Dr. Portenoy, in 1986, proposed that opiates could be used to treat chronic, nonmalignant pain without fear of addiction.
- 2. In 1996, he helped write a consensus statement stating that there was little risk of addiction or overdose when treating chronic pain patients with long-term opiates.
- **3**. Then, in December, 2012, he stated that:
  - a) "Based on the standards of 2012, his prior years of teaching were 'misinformation';"
  - b) "There was no data on the effectiveness of long-term opiate prescribing (for chronic non-malignant pain)."
- **4.** All the time between, he was receiving funding from pharmaceutical companies.

http://hcrenewal.blogspot.com/2012/12/the-king-of-pain-recants-pharmaceutical.html

#### CHRONIC PAIN + OPIATES THE BRIG<u>HTON</u>

### EXPERIENCE

- There are reasons to be concerned about not only the safety but also the effectiveness of using opiates to treat chronic pain.
- What we see at the Brighton Center for Recovery is that patients often will feel better after being taken OFF opiates.

## • WHY?

How much of the present pain is due to side effects?

CHRONIC PAIN + OPIATES THE BRIGHTON

### EXPERIENCE

- Side effects of opiates:
  - **1.** Constipation
  - 2. Loss of libido/erectile dysfunction
  - **3.** Amenorrhea
  - 4. Insomnia/Sleepiness
  - **5.** Difficulty urinating
  - 6. Nausea/vomiting
  - 7. Itching
  - 8. Headache

How much of the present pain is due to withdrawal?

CHRONIC PAIN + OPIATES THE BRIGHTON EXPERIENCE

- Withdrawal symptoms:
  - 1. Diarrhea
  - 2. Hot/cold spells and sweats
  - **3.** Lethargy
  - 4. Insomnia
  - **5.** Restless legs
  - 6. Nausea/vomiting
  - 7. Abdominal cramping
  - 8. Anxiety/Depression/Irritability
  - 9. Yawning, sneezing, runny eyes, runny nose
  - **10.** Muscle aching and soreness
  - **11.** Bone pain
  - **12.** Headache

How much pain is due to depression?

CHRONIC PAIN + OPIATES

THE BRIGHTON EXPERIENCE

- Depression oftentimes accompanies chronic pain and worsens the experience of pain.
- Opiates
  - 1. Can cause depression (80% risk after 2 years on opiates);
  - 2. Can prevent anti-depressants from being effective (mediated by kappa receptor?)

#### How much pain is CAUSED by opiates?

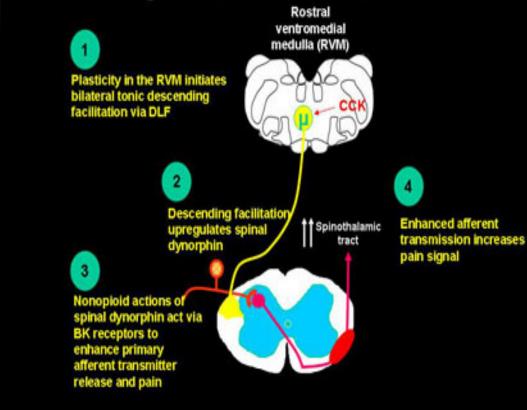
 Chronic opiate administration can cause an imbalance between the centers in the brain that regulate the experience of pain in such a way that increasing doses of opiates will actually produce MORE pain.

#### CHRONIC PAIN + OPIATES

THE BRIGHTON EXPERIENCE Opioid-induced hyperalgesia: Pathophysiology and clinical implications; Sukanya Mitra MD; Journal of Opioid Management 4:3 May/June 2008

OPIOID-INDUCED HYPERALGESIA

CHRONIC PAIN + OPIATES THE BRIGHTON EXPERIENCE Descending Facilitation, Opioid-Induced Pain



#### How much pain is CAUSED by opiates?

#### CHRONIC PAIN + OPIATES THE BRIGHTON EXPERIENCE

- This hypersensitivity to pain can result in:
  - Small painful sensations becoming BIG pain sensations (Hyperalgesia);
  - Normally non-painful sensations becoming painful sensations (Allodynia).

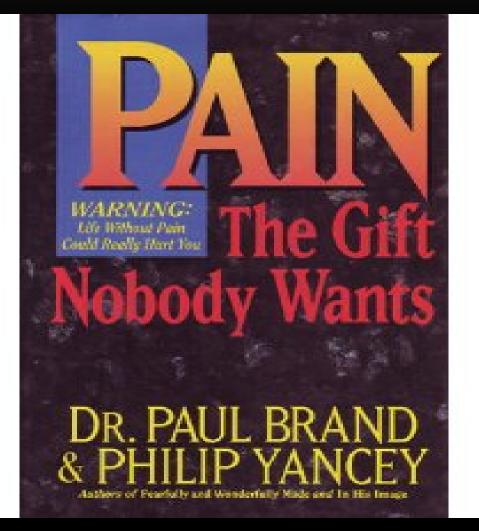
A Comprehensive Review of Opioid-Induced Hyperalgesia; Lee, Marion et al; Pain Physician: 2011, 14:145-161

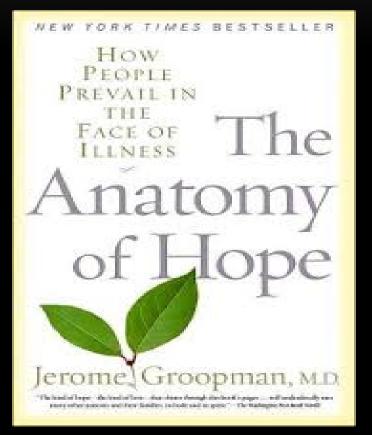
# It is not normal to live without pain.

#### **OPIATES** and **MEDICINE**

Where are we, America?

#### **CHRONIC PAIN + OPIATES THE BRIGHTON EXPERIENCE**





Chronic opiate use alone does not address the real issues in healing from injury or illness.

#### CHRONIC PAIN + OPIATES THE BRIGHTON EXPERIENCE

### **OPIATES, ADDICTION** AND **CHRONIC PAIN** WHERE ARE WE, AMERICA?

- OBJECTIVE 4
- MEDICAL TREATMENT OF ADDICTION





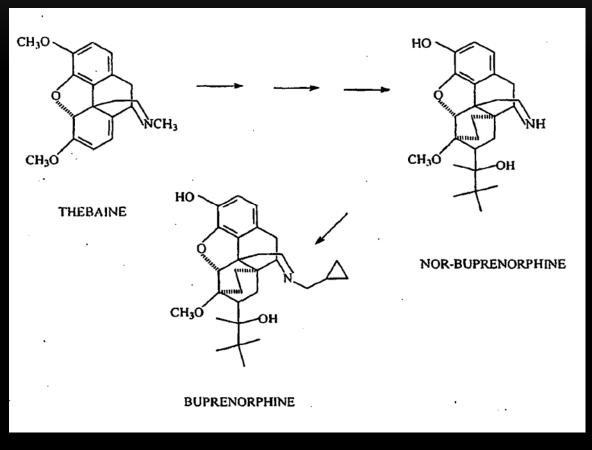


WHERE ARE WE, AMERICA?

- Morphine
  - Hydromorphone
  - Diacetyllmorphine (Heroin)

#### • Codeine

- Hydrocodone
- Thebaine
  - Group 1
    - Oxycodone
    - Oxymorphone
  - Group 2
    - Nalbuphine
    - Buprenorphine
  - Group 3
    - Naloxone
    - Naltrexone



- Suboxone contains 2 drugs, both derived from thebaine:
  - 1. Buprenorphine
  - 2. Naloxone



WHERE ARE WE, AMERICA?

 Naloxone, manufactured by Sankyo Pharmaceuticals, was introduced in the 1960's as a treatment for opioid overdose.





WHERE ARE WE, AMERICA?

• Buprenorphine itself was developed by Reckitt in the 1980's. It was a flop as a pain medicine (Buprenex).

It was re-introduced in 2003, following amendment of the Harrison Narcotic Act, for the treatment of opiate dependency. The following properties were promoted; it was seen as an exciting new treatment for opiate dependency:

1. Partial agonist = No high

- 2. Tight affinity for Mu opiate receptor = Blockade of other narcotics
- 3. Long Half-life = Once a day dosing

4. "The slow dissociation of buprenorphine from the receptor results in a long duration of effect and also confers another advantage in that when the drug is withdrawn an abstinence syndrome is rarely seen because of the long time taken for the drug to come off the receptor (Bickel et al. 1988)."

5. The addition of naloxone would prevent (or discourage) abuse of the drug.

WHERE ARE WE, AMERICA?

- Partial agonist means you can't get high...
- From hgb on Erowid:
  - I was prescribed 8mg of suboxone per day (which is quite expensive without insurance) and went home as quick as I could and slid a pill under my tongue. Within 40 minutes my withdraw symptoms were completely gone and I was in such a great mood! I had so much energy BUT this sure did and does feel like being high on a nice dose of vicodin. I got home and just grabbed the lawnmower and mowed the grass, came inside and said to myself 'now what' with all this energy. I called my wife (not telling her how high I felt) telling her it's the greatest drug in the world my withdraw symptoms are gone.

I just took another 4mg about 2.5 hours ago and feeling very high. Hard to concentrate and even type this and have read so much that this doesn't get you high. A friend said it got him a little high the first time and then just felt normal afterwards so who knows......but right now this is unreal.

- Tight affinity for the Mu opiate receptor means blockade of other opiates...
- But...
  - Effective blockade of other opiates reliably occurs only at the 16 mg daily dose.
  - The blockade is only effective for opiates, no blockade of alcohol or Xanax or cannabis or cocaine.
  - Only blocks opiates if you take it every day.

- Long half-life means once a day dosing...
- Well, 2 times a day is still less than 3-4 times a day...

WHERE ARE WE, AMERICA?

"The slow dissociation of buprenorphine from the receptor results in a long duration of effect and also confers another advantage in that when the drug is withdrawn an abstinence syndrome is rarely seen because of the long time taken for the drug to come off the receptor (Bickel et al. 1988)."

But there is a downside. This stuff has, without any doubt, worse withdrawal than heroin. The withdrawal feels different, and lasts about 4 WEEKS. My doctor says this is not uncommon, but still on the bad side of the withdrawal spectrum. The first week of withdrawal (this was after tapering down to 1mg) was hell. NO sleep at all for the entire week. I spent 7 days in bed sweating rivers and changing clothes constantly. The anxiety was unbearable. All I wanted in the world was a xanax. After that week I started to regain my ability to sleep (but it was the full month before I could really sleep through a night without sweats). I ended up getting seriously into other drugs in my desire to stay away from opioids. My Ketamine and DXM usage was seriously dangerous and very irresponsible. Every day/night for 3-4 months after quitting subutex. Either this heavy dissociative use or the withdrawal itself triggered my first manic episode. What a nut I became. But thats another story all together.

Anyway, six months later I relapsed on a whim, crashed a car and got back on subutex. And here I am unsure if I will ever try to quit buprenorphine maintenance again. I'm alive. I go to work every day. I'm safe and numb and I don't know where to go from here and I don't like where I am. brdrline (from Erowid)

- The addition of Naloxone prevents or discourages abuse of the drug...
- Well, discourages is probably accurate, but note FACT we have admitted patients addicted to IV suboxone.

- Our observations:
- Suboxone is addictive
  - It produces euphoria
  - It has a withdrawal syndrome associated with it
- Suboxone is being abused (In a recent study in the Journal of Addiction Medicine, over 60% of patients requesting treatment from a physician for Suboxone had first used it illegally):
  - It is being sold/traded on the streets for money or other drugs;
  - Tablet forms are being crushed and used intranasally and intravenously;
  - It is being used to beat drug testing (e.g. for probation);
  - Patients call in for early lost/stolen/dog ate my medication prescriptions;
  - Patients give the drug to friends/family members (a felony under federal law);

- Suboxone is particularly addictive in the opiate naïve patient
- It is difficult to be drug-free when you are taking an opiate; patients often use other drugs or drink when taking Suboxone;
- Many patients fail to engage in any Recovery work, they are satisfied with a "Suboxone Awakening" as opposed to a "Spiritual Awakening;"
- What finally drove us to stop using Suboxone at the Brighton Center for Recovery was that we began getting requests to help patients get OFF Suboxone, and found it a monumental task no matter what approach one uses.
- Suboxone fundamentally changes the Doctor-patient relationship. The physician is no longer primarily an ally on the road to Recovery, he has become , in some sense, a drug supplier.

- What role does Suboxone play at the Brighton Center for Recovery?
  - We do not use it for chronic pain. It is an opiate and has been shown to cause Opioid-induced Hyperalgesia, just like any other opiate. All the other previous considerations apply as well.
  - We do find it has utility in detoxification:
    - Good management of acute withdrawal
    - Post-acute withdrawal is manageable if acute withdrawal is handled well.

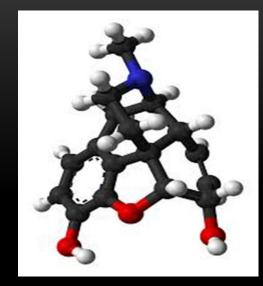
WHERE ARE WE, AMERICA?

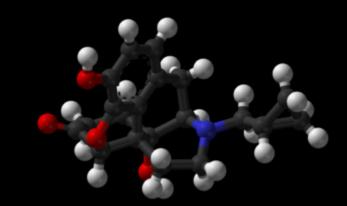
#### • Morphine

- Hydromorphone
- Diacetyllmorphine (Heroin)
- Codeine
  - Hydrocodone

#### • Thebaine

- Group 1
  - Oxycodone
  - Oxymorphone
- Group 2
  - Nalbuphine
  - Buprenorphine
- Group 3
  - Naloxone
  - Naltrexone





WHERE ARE WE, AMERICA?

# Vivitrol

- Contains only one drug Naltrexone
- Naltrexone is related to Naloxone. It is not a narcotic, not a controlled substance, does not produce euphoria, does not have any withdrawal associated with it.
- Naltrexone in this form is administered once a month by injection.
- It helps to curb opiate cravings, probably much more effectively than the oral formulation.
- Many people relapse when they stop taking it.

