Rx OPIOIDS-Friend or Foe

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OPIOIDS...Friend or Foe?
Making the Numbers Work

I didn’t have any accurate numbers so I just made up this one.

Studies have shown that accurate numbers aren’t any more useful than the ones you make up.

How many studies showed that?

Eighty-seven.
Rx Alcohol
60’s and 70’s
80’ and 90’s
Now...Some Old-Some New
Perception is Reality

Can you get me some failure estimates for our next gen product?

I can if you like numbers that are based on hallucinated assumptions.

I kind of do.

I think we have an understanding.
Headlines – “Epidemics”- Politics

According to the CDC, a dramatic increase in opioid prescriptions has led to “skyrocketing” rates of overdose deaths & addiction. Drug overdoses are now killing more Americans than car crashes.

The Opioid Analgesic Epidemic: How it Happened

Unintentional Drug Poisoning Deaths Involving Opioid Analgesics, Cocaine and Heroin: United States, 1999–2011

Health care providers wrote 259 million prescriptions for painkillers in 2012, enough for every American adult to have a bottle of pills.
“And the survey says…”
The following slides are a brief demonstration of how easily numbers can be manipulated to say what you want them to say. Hopefully this will give you some idea of what is real and what should be questioned.

Such “Diversions” and deceptions keep us from putting our best effort toward preventing, reducing and stopping **all** substance abuse.

As we work towards this goal it is imperative that those who actually benefit from Rx opioids be allowed to get them without being demonized, stigmatized or treated like a criminal.

This group of > 100 million sufferers are almost always inhumanely left out the discussion.
CDC REPORTS...2013

~16,000=Involved Opioid pain relievers or Opioids Contributed to death

“Deaths involving both illicit and Rx drugs are included in BOTH categories”
This means that BOTH categories have inflated numbers (>50% have both)

Blood levels varied with each individual and MOST (~75%) died from a lethal COMBINATION of drugs. Any trends calculated from this data should be considered “DEATHS CAUSED BY DRUG COMBINATIONS”

“When multiple drugs are found in autopsy toxicology reports, the most likely cause of death will be the accumulated damage of combination drug use-NO SPECIFIC DRUG CAN BE BLAMED FOR THIS”
NIH-CDC “Caveats”

(Public Heath Reports/July-August 2010 / Vol. 125...Leonard Paulozzi – CDC)

“These results should be interpreted with caution for several reasons

“The accuracy of the findings depends on the accurate categorization of overdose as a cause of death on death records”

“Similarly, it is possible that growing awareness of overdose as a public health Px may increase the likelihood that deaths are categorized as overdoses”

“Additionally the available data from CDC do not allow for determination of the extent to which the overdose was due to specific substances”

“More broadly the observational nature of these analyses does not allow for the determination of what specifically caused the increased rates of overdose...”
The CDC Numbers Are:  

(1st #=2013   (#)=2008)

22,700 (27,153) = Deaths from ALL Rx Meds
16,235 (14,800) = Deaths from “Rx Opioids”
~9000 (9000) Involved Morphine-Hydrocodone-Oxycodone
  ~4500 (5000) Involved Methadone
  ~2700 (800) Involved “Other Rx Opioids”

~14,000 (8500) = Deaths from ALL Illicit Drugs
  ~5000 (5100) Involved Cocaine
  ~8500 (3000) Involved Heroin
  ~500 (400) Involved “Other Illicit Drugs”

** Historically this has always been low despite the media-government hype

Morphine is a metabolite of Codeine-Morphine and Heroin therefore there is often uncertainty about the drug involved when this is found

TOTAL DEATHS:  2008 = 24,000    2013 = 30,000

•  “Deaths from Rx opioids now exceed deaths from heroin and cocaine combined
To put things in perspective…

There were approximately 2.5 million deaths in the US in 2008 and 2013.

16,000 “Opioid” Deaths = 0.6% of Deaths  
30,000 NSAID Deaths

9000 Morphine-Hydrocodone-Oxycodone deaths = 0.4% of Deaths

5000 Actual “Opioid Only” Recreational Deaths = 0.1% of Deaths

500,000 Tobacco and Alcohol Deaths = 20% of deaths

There were ~ 256 million Rx for Opioids = Death rate of 0.000019 per Rx

100,000 Rx med Deaths-Any Cause  
40,000 “Known Suicides”

So which “epidemic” is causing the most harm and costing the most money and which creates Drama - Fear and Demons.
Rx Opioid Epidemic

Number of deaths (thousands)

Tobacco: 400
Diet/activity patterns: 300
Alcohol: 100
Microbial agents: 90
Toxic agents: 60
Firearms: 35
Sexual behavior: 30
Motor vehicles: 25
Illicit use of drugs: 20
“Narcotic Demons”

Legal = “Opium / derivatives and their semi/fully synthetic derivatives as well as Cocaine, Coca leaves, Marijuana, Methamphetamine and Barbiturates”

Not a synonym for “Opioid”…Use demonstrates Bias-Stigma-Poor Understanding

Linked to…Contribution to…Associated with or Increased risk of DOES NOT MEAN:
Died because of…Killed by or Cause of Death

Does’t even mean that opioids were found on Toxicology report

“Milkshakes are linked to / Associated with / Involved with / Increases risk of Diabetes”
Why Abuse?

**EUPHORIA:** Feels VERY Good...Far Beyond Normal Pleasure

**ADDICTION:** Euphoria becomes Emotional Important

**AVOID W/D:** Nasty...Afraid to Quit...Physical Dependence NOT Addiction

**EMOTIONAL ISSUES:** Dysphoria...Depression...Dysthymia...Anxiety...Emotional Agony

**THESE PEOPLE CAN QUICKLY “FALL in LOVE” with OPIOID “Relief”**

**ENDORPHIN ISSUES:** Born this way or Damaged by High-Dose Opioids?...Depression
These people feel “Normal” when using so it “Makes Sense”

**UNDERTREATED PAIN:** Toxic Abnormal State and will do anything for “Relief”
Opiophobia...Physical Dependence NOT Addiction...Bias
Many Ways to Use
Endogenous Opioids - Receptors

**Endorphin-Morphine**

![Chemical structure of Endorphin-Morphine](image)

**Table 1. Opioid Receptor Activity**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (µ)</td>
<td>Supraspinal and spinal analgesia, euphoria, miosis, sedation, constipation, respiratory depression, addiction, hormonal changes</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Supraspinal and spinal analgesia, diuresis, sedation, miosis, dysphoria, psychomimetic effects, respiratory depression, constipation</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Supraspinal and spinal analgesia</td>
</tr>
</tbody>
</table>

*Source: References 4, 5.*

**Opiate Receptors In The CNS**

- Thalamus
- Hypothalamus
- Pituitary glands
- Periventricular nuclei
- Periaqueductal grey
- RAPHE MAGNUS Enkephalin (δ)
- Spinal cord: Dymorphinergic neuron with κ receptors
- Presynaptic inhibition of both III and IV fibres by enkephalins
- Pain inhibitory complex: enkephalin (δ)

*Fig. 3-10*
How Opioids Work

Decrease Perception of Physical and Emotional Pain

Message is Altered...Not as Important...”Don’t Care”
Antitussives:
Mechanism of Action

Opioids
- Suppress the cough reflex by direct action on the cough centre in the medulla

Examples:
- codeine
- hydrocodone

Mechanism of Cough

Stimulation of mechano- or chemoreceptors (throat, respiratory passages or stretch receptors in lungs)

Afferent impulses to cough center (medulla)

Efferent impulses via parasympathetic & motor nerves to diaphragm, intercostal muscles & lung

Increased contraction of diaphragmatic, abdominal & intercostal (ribs) muscles ⇒ noisy expiration (cough)
Opioids Stop GI Movement
Stop Diarrhea and Cause Constipation
Areas Involved in Depression-”Melancholy”

Anatomy of the Brain

- Frontal lobe
- Parietal lobe
- Occipital lobe
- Temporal lobe
- Amygdala
- Hippocampus
- Cingulate gyrus
- Thalamus
- Fornix
- Parahippocampal gyrus
- Medulla oblongata
- Pons
- Cerebellum

Opiate Receptors In The CNS

- Thalamus
- Hypothalamus
- Pituitary glands
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- RAPHE MAGNUS Enkephalin (S)
- SPINAL CORD: Dymorphinergic neuron with δ receptors
- Presynaptic inhibition of both III and IV fibres by enkephalins
- Pain inhibitory complex: enkephalin (S)

Frontal cortex
- Anterior cingulate cortex (ACC)
- Dorsolateral prefrontal cortex (DLPFC)
- Orbital frontal cortex (OFC)

Hypothalamic-pituitary-adrenal (HPA) axis
- Nucleus accumbens
## Opioid Maintenance Therapy (OMT)  
### Opioid Antagonist Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism at Opiate receptor</th>
<th>Dosage</th>
<th>Contraindications</th>
<th>Pregnancy</th>
<th>Office-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone (Methadose)</td>
<td>Agonist</td>
<td>50-120 mg PO qd</td>
<td>Methadone hypersensitivity</td>
<td>Safe Neonatal withdrawal syndrome</td>
<td>No+</td>
</tr>
<tr>
<td>Buprenorphine (Subutex)</td>
<td>Partial Agonist</td>
<td>8 to 24 mg PO qd to 3x/wk</td>
<td>Buprenorphine hypersensitivity</td>
<td>Safe* Neonatal withdrawal syndrome</td>
<td>Yes#</td>
</tr>
<tr>
<td>Buprenorphine-Naloxone</td>
<td>Partial Agonist-Antagonist</td>
<td>8 to 24 mg PO qd to 3x/wk</td>
<td>Buprenorphine or naloxone hypersensitivity</td>
<td>No</td>
<td>Yes#</td>
</tr>
</tbody>
</table>
| Naltrexone (Depade, ReVia)| Antagonist                   | 50 mg PO qd to 3x/wk          | Liver failure  
Active opioid use Naltrexone hypersensitivity | No                          | Yes           |

+ Certain physicians who work closely with an opioid treatment program may prescribe methadone

* Preliminary studies indicate buprenorphine is safe in pregnancy, but methadone is better studied in pregnancy and should be presented as an option to women who become pregnant while on buprenorphine therapy.

# Qualified physicians need to apply for a waiver in order to prescribe buprenorphine for opioid dependence.

^ Buprenorphine-Naloxone is available in 2 fixed dose preparations: 2 mg buprenorphine-0.5 mg naloxone and 8 mg buprenorphine-2 mg naloxone.
Under Treatment of Pain
Bad Stuff Happens

Persistent Pain

Time off work, money worries, relationship concerns
Negative thinking, fear of the future, depression/mood swings
Weight gain/loss
Stress/fear/anxiety/anger/frustration

Sometimes the arrows can also go anti clockwise as well. For example - time off work can lead to negative thinking fear of the future - can lead to stress, fear etc

Being less active
Loss of fitness, weak muscles and joint stiffness
Create ‘no go’ lists of things you cannot do
Sleep problems/tiredness/fatigue
UNRELIEVED PAIN CAN CAUSE as MANY or MORE PROBLEMS as ADDICTION or SIDE EFFECTS

INCREASE:
Use of NSAIDS (Ibuprofen-Naproxen-Voltaren-Celebrex) = >GI-Renal and Cardiac Px
Use of ACETAMINOPHEN (Tylenol, et.al.) = Liver Px
EMOTIONAL Px = Depression-Hopelessness-Give up-Anxiety-Resentment-Insomnia
Made to feel like an “Addict” or “Criminal” when filling meds
ALCOHOL-DRUG USE = Self-medication esp. with Alcohol, Benzo’s and Marijuana
DEATH RATES = Pain Kills and Makes it OK to Die…Many “Suicides”-”Accidental OD”
>Risk of Heart Attack-Stroke-High BP-Stress

DECREASE:
QUALITY of LIFE = Suffering…Weakness…<Mobility
WORK = Lost Wages…<Quality of Work
PLAY = >Relationship Issues…<Sex and Sex Play…<Energy…<Independence…Isolation
HEALTH = Pain Interferes with Healing…<Mobility…>Obesity…Muscle Atrophy

You will be seeing more clients in this category:
Aging Baby Boomers…Surgery/Injury/War/Disease Survivors
Most are not Addicts and will have a poor response to Treatment-AA-NA
“Pseudo” or “Real” Addiction
Pseudo-Addiction or Abuse

Group of behaviors that are caused by poorly controlled pain. At first glance it looks like “Aberrant Drug-Seeking Behavior”. Source of many Pain Myths. In reality it occurs when the person will do almost anything for relief of pain… Px disappear if pain is better controlled. Educate patient: ”Pain-Free is Impossible”

Such lists are better suited to evaluate pain control than to ID “Aberrant Behaviors”

**DRUG HOARDING** = Fear of running out…Saves meds for worst pain or to abuse?

**UNAUTHORIZED DOSE INCREASES-EARLY REFILL** = Tolerance…Disease Progression…Abuse?

**MULTIPLE Dr’s** = “Dr. Shopping?”…Poor Tx…Insurance Px

**INTERNET-STREET PURCHASES** = Inadequate pain control…ALWAYS a BAD CHOICE

**ALCOHOL-’WEED USED for PAIN** = Inadequate pain control…ALWAYS a BAD CHOICE

**TRADES MEDS** = Not good but doesn’t tell you much…Common in many families

**DEMANDS** = More/Different/Specific Brand Meds…Desperate for relief

**PAST Hx of ABUSE** = Very Poor Pain Indicator…Bias without Justification…Abusers have legit pain too

**CLOCK-WATCHING** = Effort to comply with Directions…Sign of breakthrough pain

**MANIPULATION-LYING** = Learn what will give them relief

**NON-PAIN RELATED OPIOID USE** = Sleep Issues…Futile attempt to treat depression

**ENJOYS MEDS** = Relief makes you feel better…Getting High or Decreases Suffering?

**ALWAYS TIRED** = Dosage too high…Takes energy to deal with pain…Poor Sleep/Rest

**MOOD SWINGS** = Pain makes you ill/Resentful…”Why grumpy old men are grumpy”

**GETS SICK if DOSE is MISSED** = This is PHYSICAL DEPENDENCE and is normal and expected
Benefits of Properly Treated Pain

Quality of Life improves in many ways:

**WORK-SOCIAL**: Can get and keep a job…>Quality of work…>Skills…>Cooperation
More Patience…Less Isolation…>Active in Community…>Friends

**FAMILY**: Respect…<Damaging Arguments…>Communication/Patience…Helpful…Fun

**PARTNER**: Intimacy…Sexual fun…Emotionally Available

**EMOTIONAL**: Less Depression…Improved Mood…Patience…Hope…Emotionally Attach

**HEALTH**: Less Stress-Agitation-Impulsive Anger-Fatigue…Improved Metabolic Process
Improved Healing…< Muscle Atrophy…<Chance of Chronic Pain Syndrome

**BRAIN**: Function/Repair Improves…Improved Emotional Control…<Confusion

**ADDICTION**: Risks Decrease…Less “Aberrant” Behaviors/Self-Medication
Addiction = Brain Disease - Loss of Control

Pleasure + Emotional Attachment

Under Subconscious-Limbic Control
Tolerance = Liver-Receptor Px

Oxidation (Cytochrome P450's) → Drug

Conjugation (Glucuronidation etc.)

Metabolite → Conjugation

Stable Adducts

Non-polar Species

Polar Species

Renal Elimination (Urine)

Biliary Elimination (Stool)

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Physical Dependence is not Addiction
Physical Dependence

Distinguishing Dependence, Tolerance, and Addiction

- Physical dependence: withdrawal syndrome arises if drug discontinued, dose substantially reduced, or antagonist administered
- Tolerance: more drug needed to maintain therapeutic effect, or loss of effect over time
- Pseudoadddiction: behavior suggestive of addiction, but due to non-optimal dose or dosing schedule
- Addiction (psychological dependence): psychiatric disorder characterized by continued compulsive use of substance despite harm

OxyContin® Tablets
(oxycodeone hydrochloride controlled-release)
Nice Stuff

Anatomy of the Brain

Hippocampus

Limbic System

Amygdala

Thalamus

Cingulate gyrus

Fornix

Parahippocampal gyrus

Occipital lobe

Temporal lobe

Frontal lobe

Parietal lobe

Pons

Medulla oblongata

Cerebellum

Neocortex

Language

Morality

Hippocampus

Mammalian Brain

Memory

Sociability

Attack

Anger

Neocortex

Logic & analysis

Rational thought

Control of emotions

Lizard Brain

Breathing/temperature

Avoidance/survival

Hunger/thirst

Territoriality

Reproductive drive

Emotion

Cognition

Pain

Okay
JUST A LITTLE PINPRICK
THERE’LL BE NO MORE
BUT YOU MAY FEEL A LITTLE SICK

CAN YOU STAND UP?
I DO BELIEVE IT’S WORKING GOOD
THAT’LL KEEP YOU GOING THROUGH THE SHOW
COME ON IT’S TIME TO GO

THERE IS NO PAIN YOU ARE RECEIVING
A DISTANT SHIP’S SMoke ON THE HORIZON
YOU ARE THE ONLY COMING THROUGH IN WAVES
YOUR LIPS MOVE BUT I CAN’T HEAR WHAT YOU’RE SAYING

WHEN I WAS A CHILD I CAUGHT A FLEETING GLIMPSE
OUT OF THE CORNER OF MY EYE
I TURNED TO LOOK BUT IT WAS GONE
I CANNOT PUT MY FINGER ON IT NOW
THE CHILD IS GROWN THE DREAM IS GONE
I HAVE BECOME COMFORTABLY NUMB