The analgesia-addiction interface:
Clinical and neurobiological issues

Howard L. Fields MD PhD
NIH
March 2007
Drugs Commonly Used for Chronic Pain

- Opioids
- COX inhibitors
- 5HT/NE reuptake inhibitors (* TCAs, SNRIs: Venlafaxine, Duloxetine, Tramadol*)
- Triptans (5HT1b/d agonists)*
- Anticonvulsants (pregabalin, gabapentin, topiramate, etc.)*

* ? Broad spectrum analgesics
Many patients have residual pain when non-opioid options are exhausted.

Opioids are currently the most potent, and broadest spectrum analgesics.
On the other hand

- Opioid efficacy past three months unproven
- Side effects (sedation, nausea, constipation, urinary retention)
- Tolerance and dependence (hyperalgesia)
- Abuse potential
Substance abuse: the scope

ca. 30 million heavy drinkers, 
120 million smokers
Most individuals are polysubstance users
Question for the clinician:
Why is my patient continuing to take opioids?

- Effective analgesia
- Relieve symptoms of physical dependence
- Patient has become addicted
- Substance abuse antedated treatment
- Patient never had pain
Prescription opioids: two user groups

- Pain treatment with opioids
- Prescription opioid abuse

Millions of people in both groups
The clinical conundrum

- Patient reports inadequate pain relief
- Risk of creating drug abuse.
- Patient with history of drug abuse
  - Legitimate pain complaint?
  - Deception to obtain drugs?
The Doctor’s Dilemma:
Does pain treatment cause opioid abuse?
New abuse rates relatively low when opioids used to treat CNCP

- **Mark Sullivan**— SE area Vets; Edlund et al, Pain in press.
  2% (ca. 300/15000) overall incidence (25% non-opioid Sub Abuse, 67% Mental health Dx)
Some substance abusers become opioid abusers when treated with opioids.
Know your patient

“Doc, only Dilaudid works for me.”

“Doctor, John doesn’t like to take drugs”
Patient evaluation and monitoring

- Screening instruments (Kirsch, Managed Care 16, Supplement 3, February, 2007)
- Urine toxicology
- Steve Passik: Aberrant drug taking behaviors—record keeping
The Future

- Genetic screens
- Endophenotyping, functional imaging
How can we improve pain therapeutics?

- Better non-opioid analgesics
- Non-pharmaceutical approaches (CBT, etc.)
- Opioids with reduced tolerance and dependence (DOR antagonists, adjuvants)
- Potent, non-rewarding analgesics
Properties of an Ideal Analgesic

The holy grail of pain research

- Completely safe & totally effective
- Works on all pains
- Tolerance does not develop
- Non-addicting
What about opioids; can we separate analgesia and reward?
The same receptor mediates both MOP and KO.

Opioid family of 7TMD GPCRs

MOR gene

- analgesia
- reward
- withdrawal
- respiratory depression
- immunosuppression
- constipation

Kieffer TIPS, 1999
Opioid analgesia circuit

Hughes & Kosterlitz, 1975
Basbaum & Fields, 1976
Mesolimbic reward circuit

Olds & Milner, 1954
McGill / Hebb lab
Rats self administer drugs directly into the reward circuitry

- Nucleus Accumbens
- Cocaine, amphetamine
- Opiates, ETOH, nicotine
- Dopamine neurons
Reward circuit produces analgesia

Franklin, Neurosci Biobehav. Rev, 1989
Altier & Stewart, JPET, 1998
Schmidt et al, Eur J Neurosci 2002
Psychostimulants potentiate opioid reward

Blocked by Dopamine antagonists in NAc
We need to know how the reward circuitry produces analgesia

- If we can uncouple these processes, we may have better analgesics.
Human NAc activity correlates with magnitude of monetary reward

Knutson et al, J. Neurosci 2001
Noxious stimuli and pain predictive cues activate human ventral striatum

Jensen et al, Neuron, 2003

Becerra et al, Neuron, 2001
Expectation of pain relief leads to opioid release in NAc

Zubieta et al, J. Neurosci, 2005
NAc neurons encode reward value

Sharif Taha
How is reward circuit linked to pain modulating pathway?

What are the relevant non-opioid Neurotransmitters?

Becerra et al, Neuron, 2001
Summary

• Opioids are essential for treating moderate to severe pain
• Neurobiologists are making progress in reducing opioid tolerance and dependence
• Opioids are rewarding; this has created a growing non-medical demand for prescription opioids
• Opioid addiction is a disease
• Understanding how opioids produce reward and analgesia will lead to better analgesics and treatments for addiction.
Thanks

- NIDA, NINDS and the NIH pain consortium,
- The AMA
- Allan Basbaum, Jon Levine, Mary Heinricher, Mike Morgan, ZZ Pan, Sharif Taha
- State of California Alcoholism and Addiction Research Program, Gallo Research Center, Wheeler Center, University of California