# Clinician and clinical research perspectives on opioid analgesic tolerance and hyperalgesia

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Adjunct Professor of Anesthesia, Emeritus Professor of Neurology, UCSF
Attending Neurologist, UCSF Pain Management Center

Day 1, Session 1: Clinical need and risks associated with higher daily dose and higher dosage strength opioid analgesics: Clinician and patient perspectives

# Relevant experience

1979-80 Fellowship UCSF Drug Dependence Research Lab

1982-84 Medical Director, SFGH/UCSF Substance Abuse Services
(Methadone detox and methadone maintenance clinics)

1986-88 Pain Research Fellowship with Howard Fields at UCSF

1989-on UCSF Pain Management Center Attending Neurologist
(Associate Director 1989-2009)

1989-09 Founder and Director, UCSF Pain Clinical Research Center
First placebo controlled i.v. opioid trial for neuropathic pain 1991
Opioid 8 week trial for neuropathic pain 2003
Opioid 6 month trial for chronic pain hyperalgesia pain models 2006

2009-18 Scientific Director, CPMC Research Institute (Sutter Health)

2018-on Chief Research Officer, Sutter Health

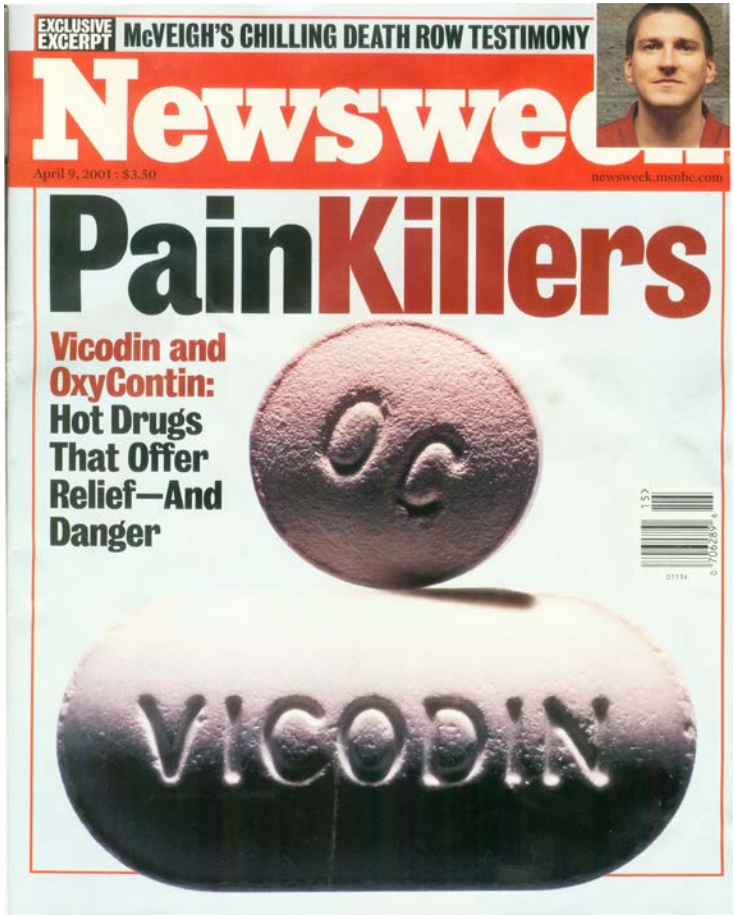
# Can opioid therapy make pain worse? 19th century perspective

"Pain, which I know is an evil, is less injurious than morphia, which may be an evil."

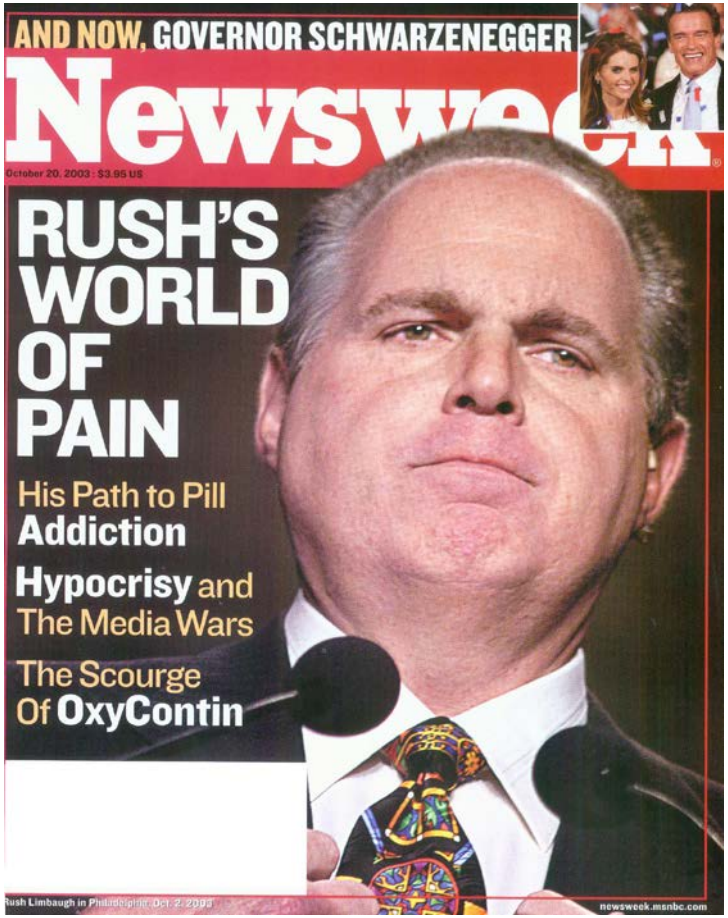
"Does morphia tend to encourage the very pain it pretends to relieve?"

Albutt C. On the abuse of hypodermic injections of morphia. *Practitioner* 1870; 5:327-331.

# The current opioid epidemic is at least 18 years old




2001




2003

Faced with an opioid epidemic of abuse, addiction, and death, “the pendulum swings from pain control to drug control” [Goesling 2019]

# Opioids are effective but…..

- Opioids – effective compared to placebo, antidepressants, and anticonvulsants (Busse et al, JAMA 2018)
- CAVEATS:
  - Little efficacy data spanning over long time periods (6 months +) for opioids or any drug class
  - Drop out rates in trials of opioids higher than for non-opioids
  - Many patients cannot tolerate mood and other effects
  - Stigma and fear of addiction leads to self-dc
  - Prescribers fear licensing board investigation and reputational damage

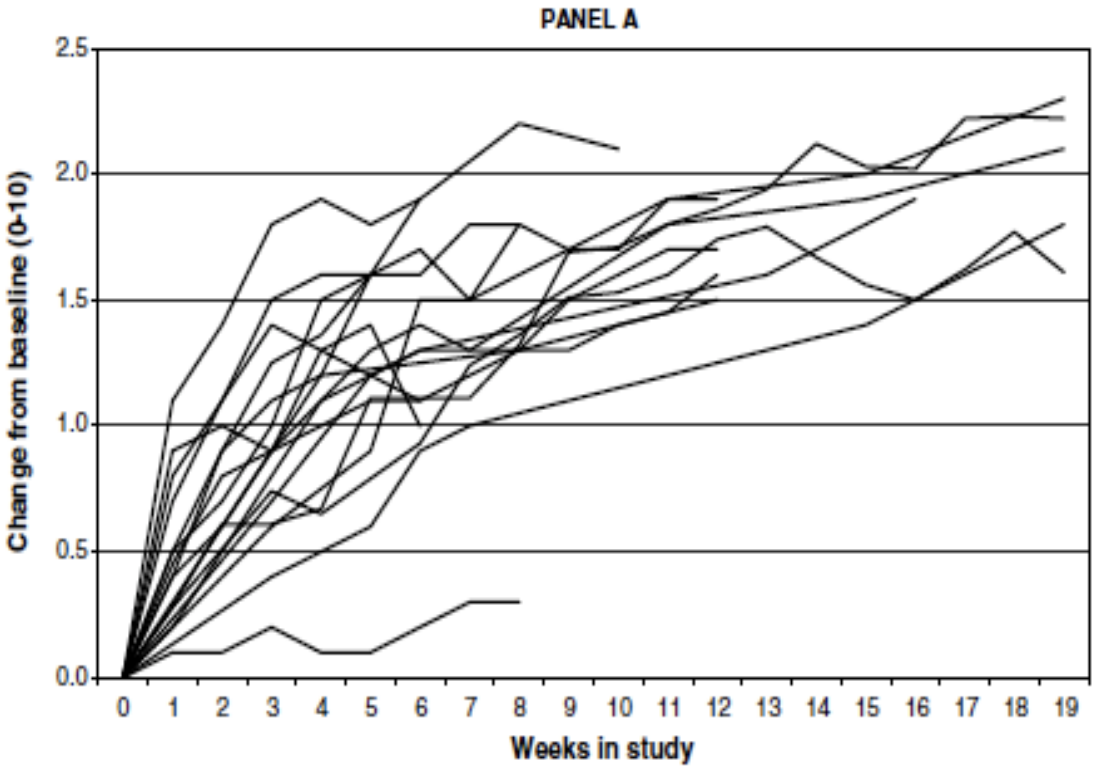
# Physicians are a big part of the problem

## Exposure to prescription opioids increases risk for opioid abuse, overdose, and other adverse events in a dose- and duration-dependent manner

- Prescribers are, directly or indirectly, the source of most misused opioids. Opioid prescribing often continues after abuse is diagnosed.
- Opioid dose predicts overdose risk. Decreasing prescribed opioid doses not yet proven to reduce risks to patients.
- Opioids plus benzodiazepines/sedatives or alcohol: 80% of unintentional opioid overdose deaths may involve benzodiazepines.
- Urine testing under-utilized. Requiring very frequent office visits before refilling Rx is both legal and ethical.

# Why is it so hard to demonstrate long-term opioid efficacy?

- Placebo response doesn't stabilize - increases over duration of study
- Confounds demonstrating long-term efficacy of **any** drug for pain



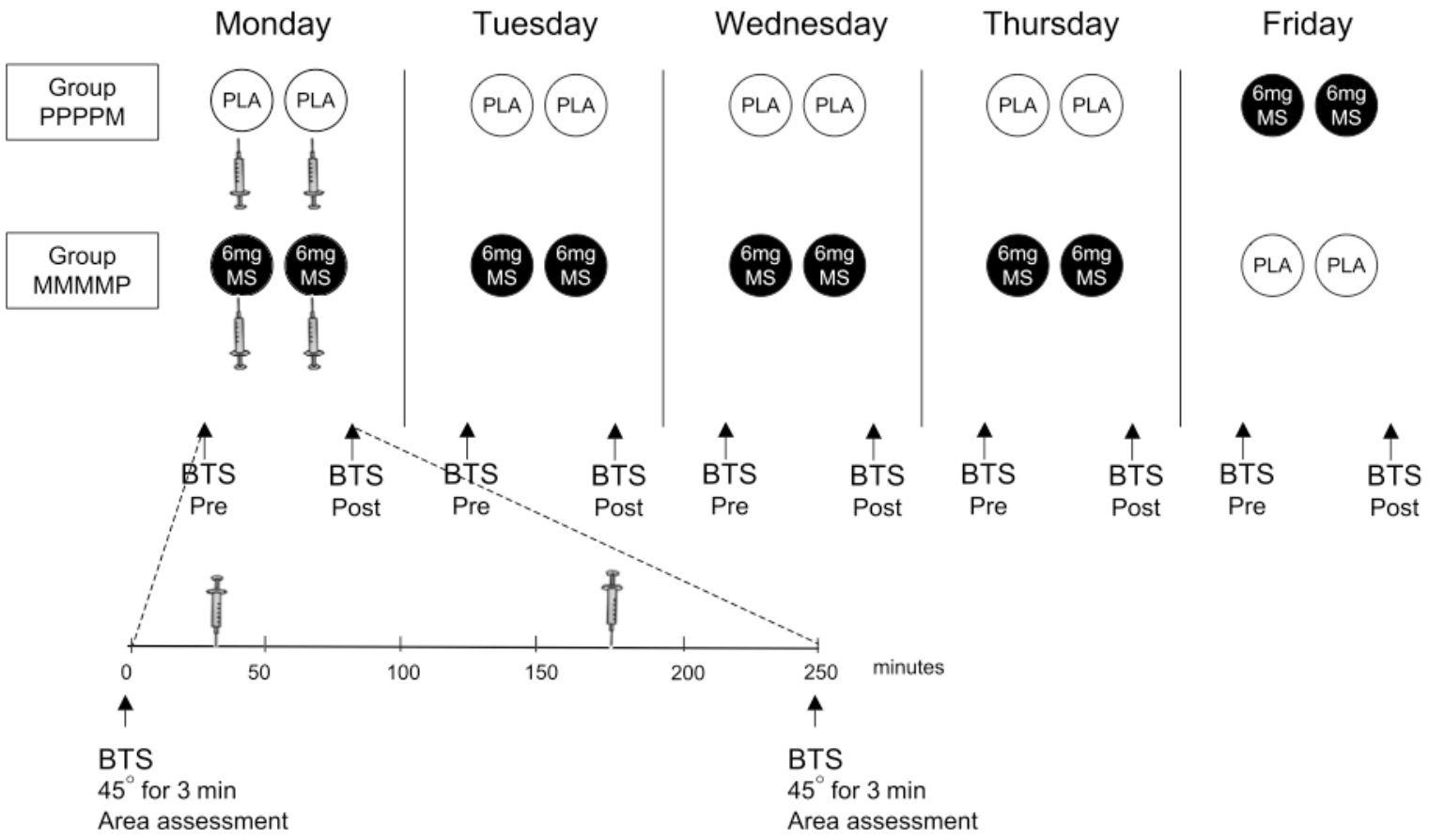

Quessy and Rowbotham 2008

# Tolerance

Dose escalation or loss of analgesic efficacy during longer term treatment of chronic non-malignant pain

# Analgesic tolerance during brief morphine therapy

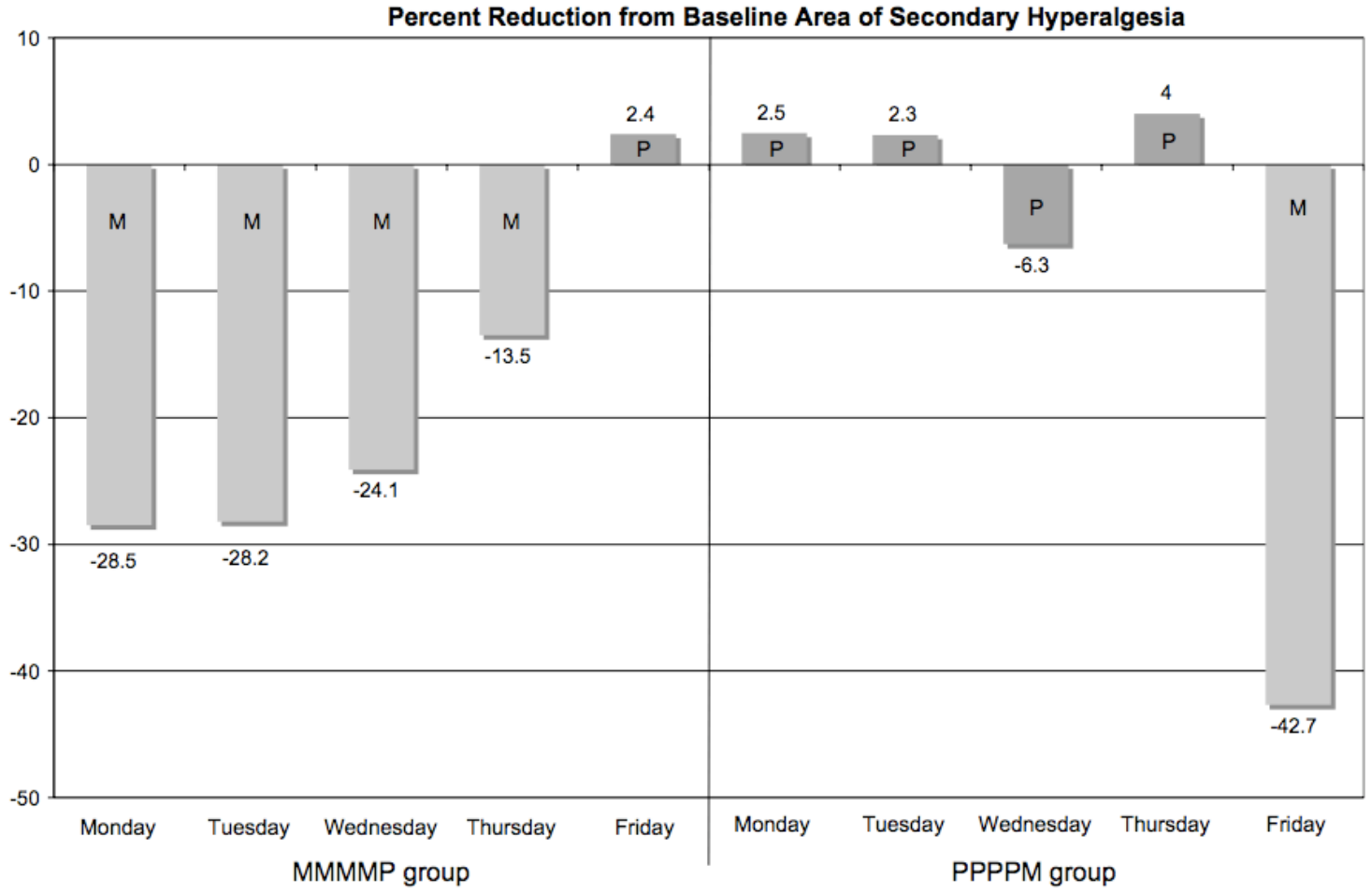
## Double-blind, placebo controlled RCT in healthy volunteers




Petersen, Rowbotham, et al, PAIN 2008

# Analgesic tolerance during brief morphine therapy

## Double-blind, placebo controlled, parallel group RCT in healthy volunteers




N= 52 p= 0.06

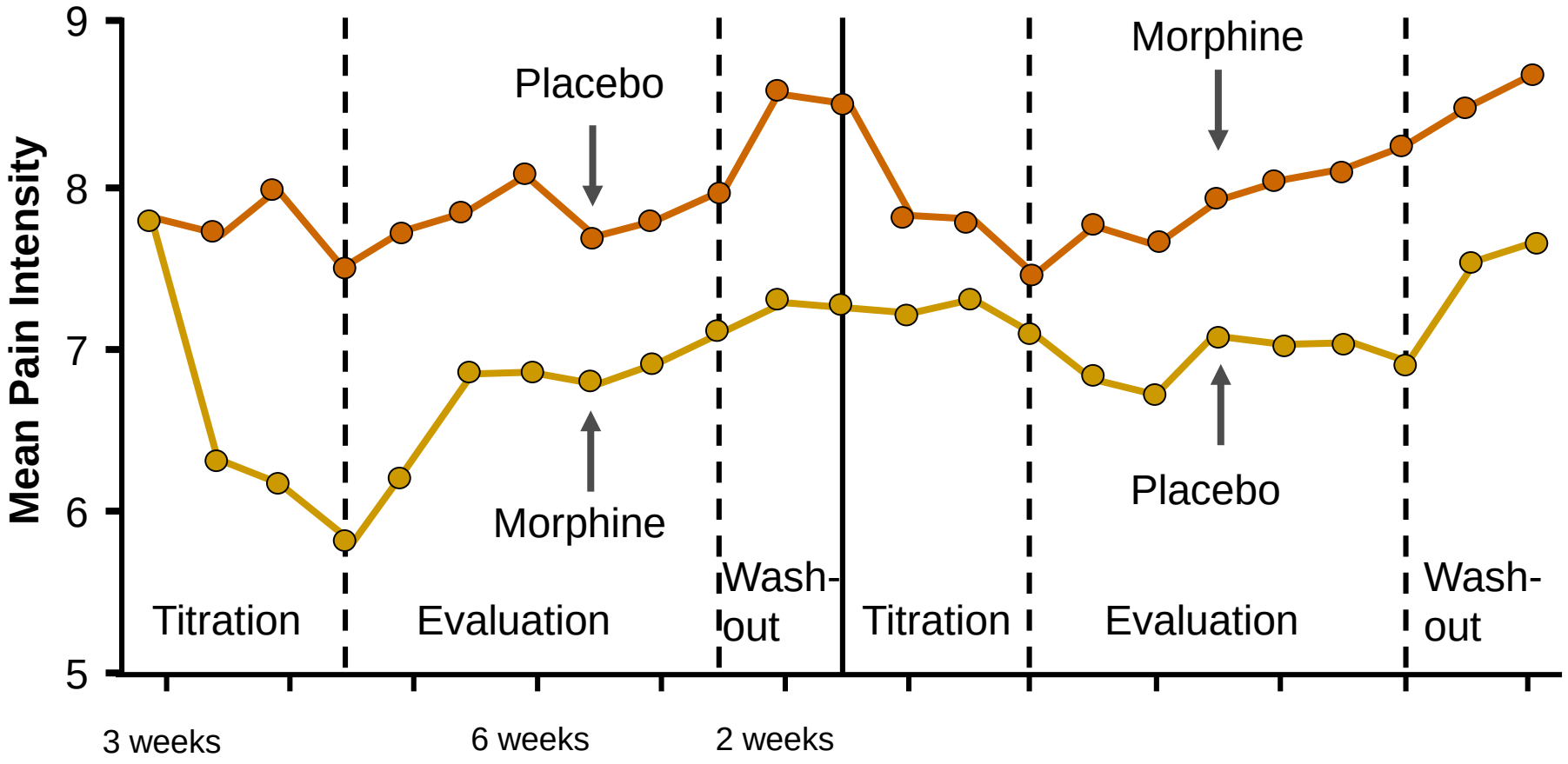
No hyperalgesia or withdrawal

Petersen, Rowbotham, et al, *PAIN* 2008

# Dose escalation and analgesic efficacy during longer term therapy

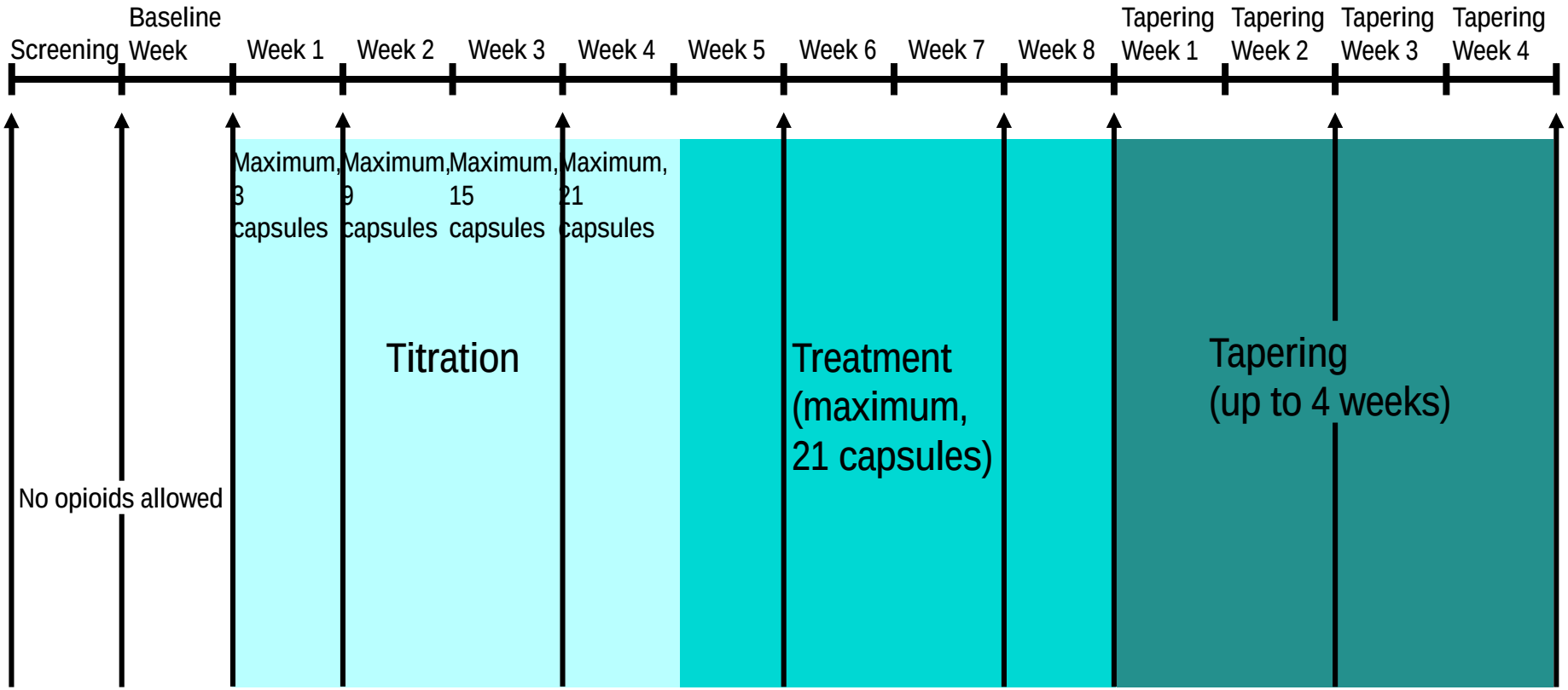
## Chronic non-malignant pain

# Daily morphine for chronic musculoskeletal pain




Moulin et al. *Lancet.* 1996;347:143-147

# Levorphanol for Peripheral and Central Neuropathic Pain: Low- vs High-Strength Levorphanol Capsules Randomized, Double-Blind Comparison



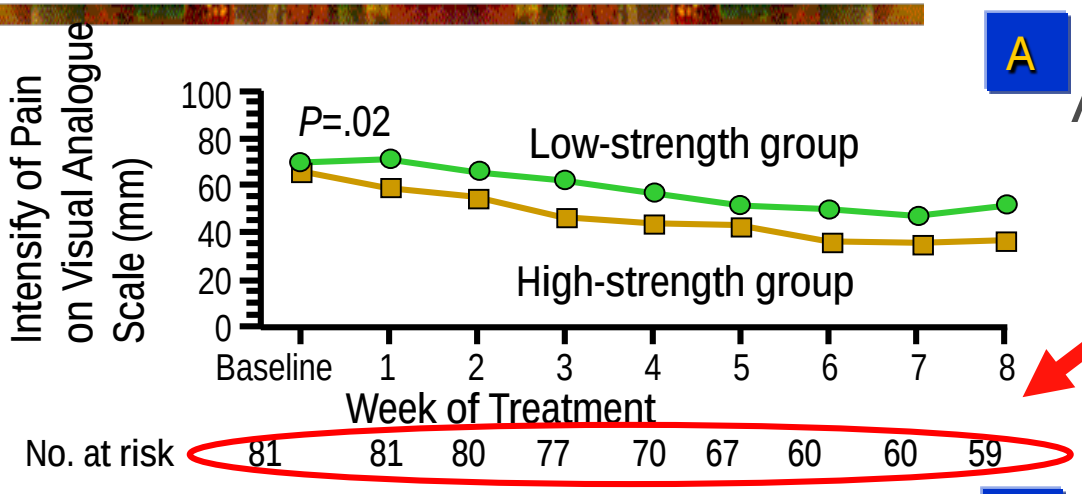

Rowbotham et al. *N Engl J Med.* 2003;348:1223-1232

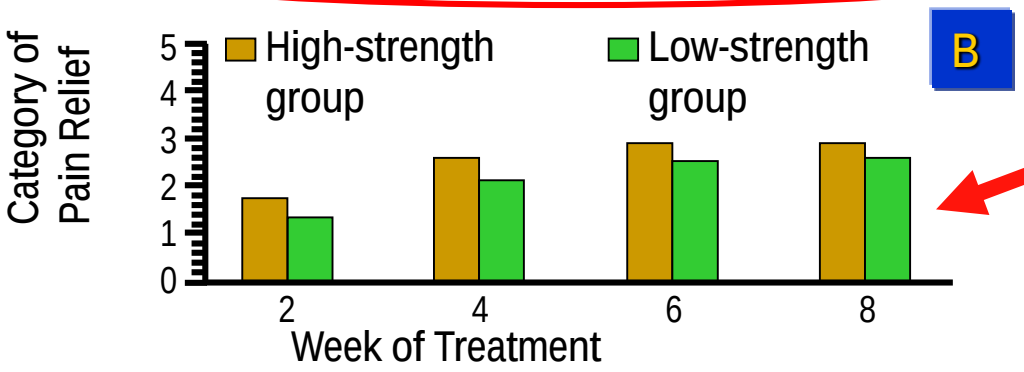
# A Closer Look…

**81 subjects randomized, 59 completed**

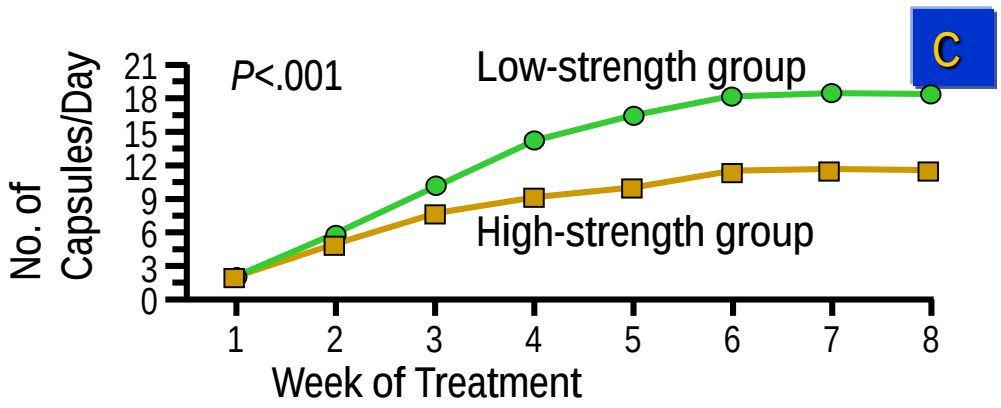
**15 drops due to AEs; agitation in high-strength group**

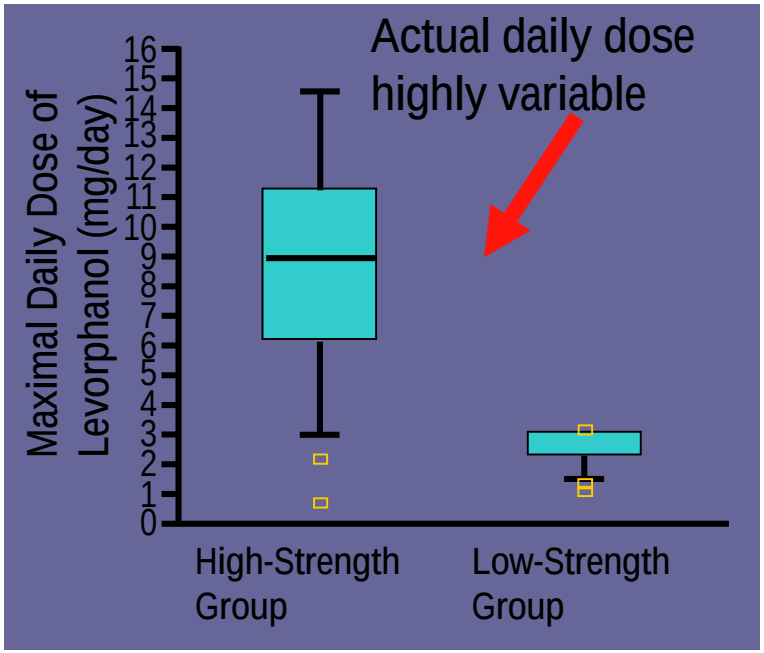
**Eventual drops fell behind early in capsule intake, pain reduction, and pain relief**




No significant group difference in relief ratings

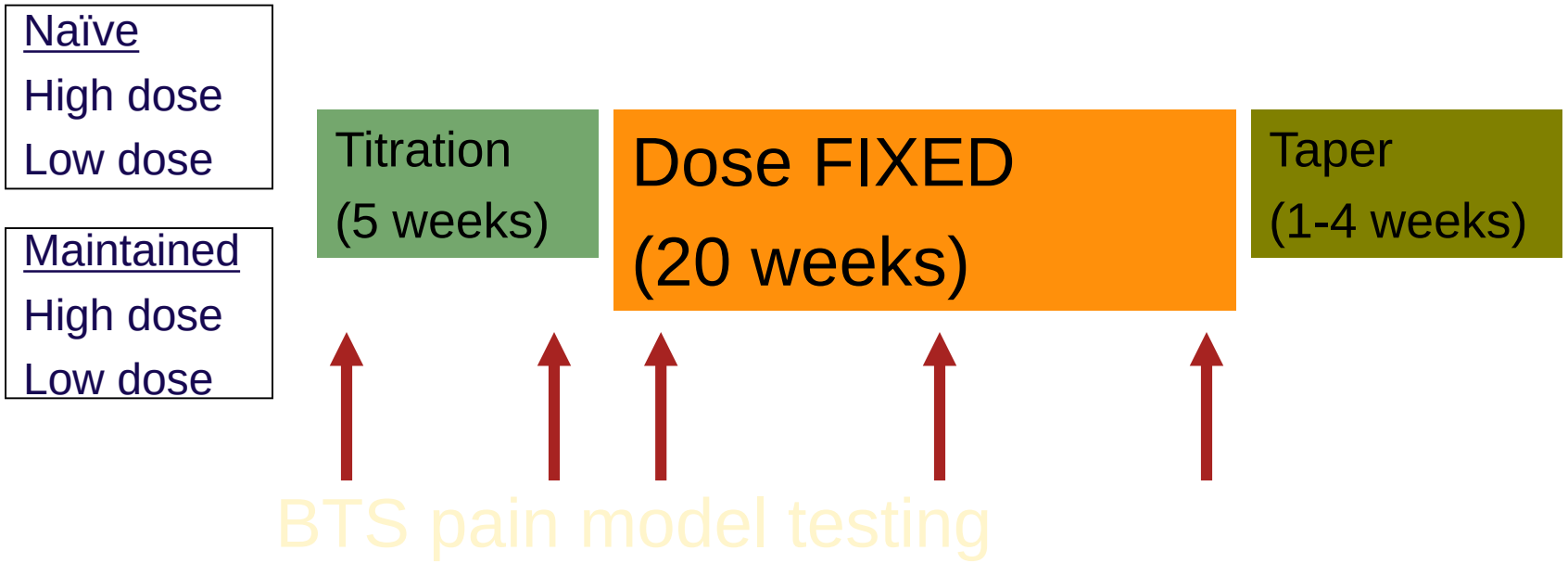


# Opioid-Induced Hyperalgesia (OIH)

- State of nociceptive sensitization caused by exposure to opioids
- Frequently invoked as major contributor to addiction, dose escalation, and overdose
- Historical data anecdotal, confounded
  - Opioid tx chronic pain & methadone maintenance cold sensitivity
- In humans, little or no prospective data to support OIH
  - Chu 2012 found tolerance but not cold hyperalgesia after 1 month
  - Rowbotham and Wallace data

# Study Design

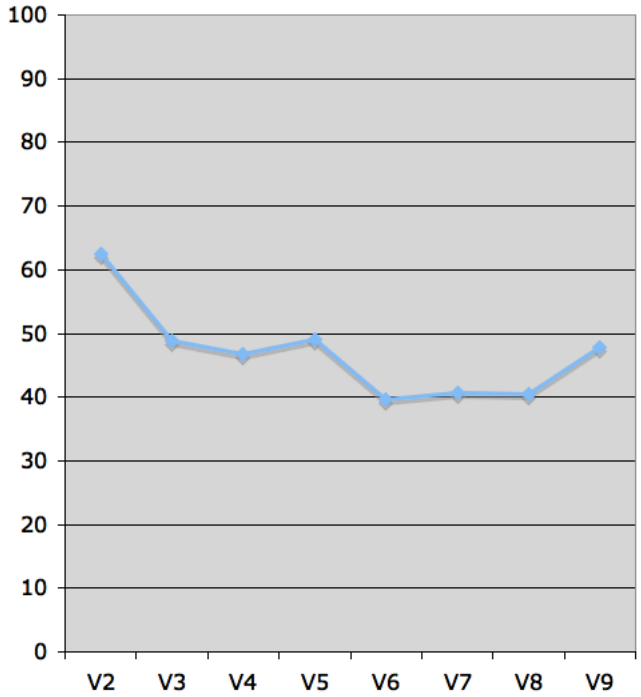



*UCSF-UCSD collaboration: Rowbotham, Petersen, Wallace*

Opioid-naïve = <30 mg/day MS  Opioid-maintained = 30-150 mg/day MS

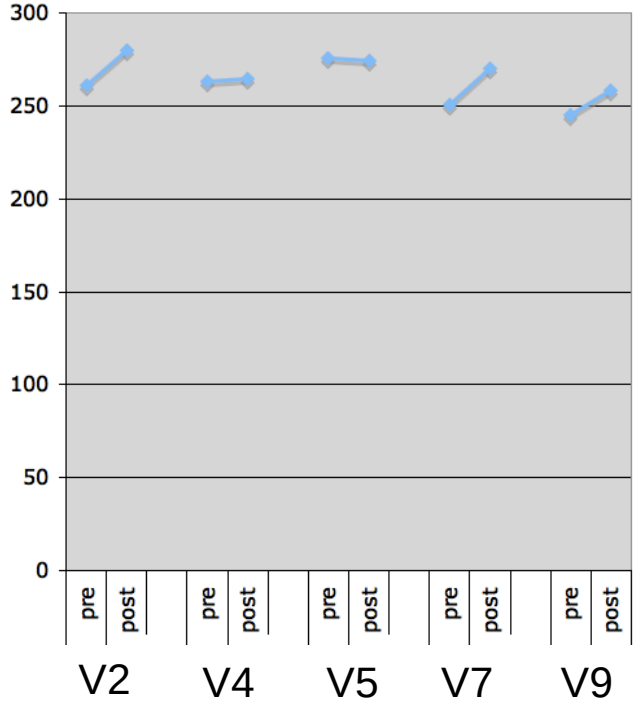
# Initiation to end of stable treatment (Day 147): 17/30 subjects completed

Pain Prior week

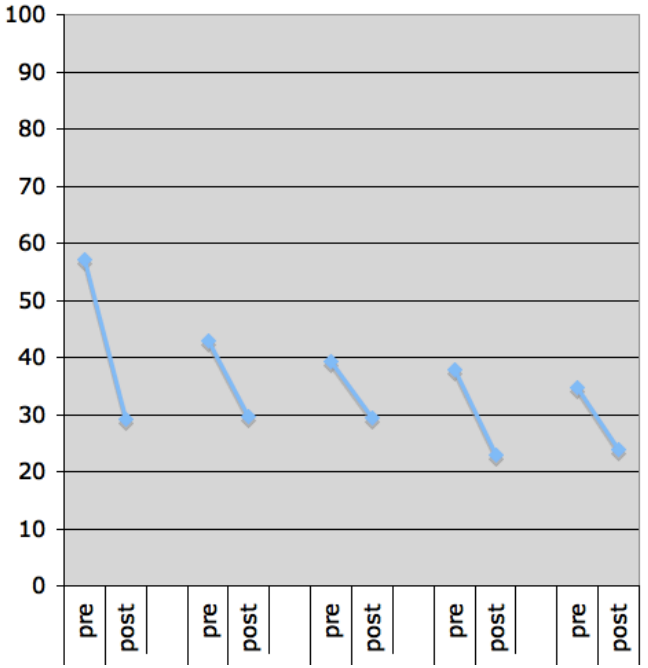



Visit number

BTS Area $mm^2$




Pain now




Final opioid dose avg 138 MEQ
Range 14-300 MEQ/day

- possible OIH in 3/17 completers:
  - Deterioration in daily pain scores = clinical deterioration.
  - At V7 - enlargement in post-dosing BTS area and increased painfulness of heating = hyperalgesia.
  - If the perceived analgesic effect at an observed dosing session (% pain relief at 90 minutes) was also reduced compared to the end of titration, it would constitute evidence of both tolerance and hyperalgesia.

# 5 takeaways

- Who should receive opioids? Chronic pain patients treated with opioids are not that different from methadone maintenance patients
- The hardest part of tapering off opioids for patients is starting; a complete taper is often an unrealistic goal
- Clinicians struggle to set limits and monitor patients closely; slow to recognize dependence and abuse, toxic combinations of opioids and sedatives/alcohol
- What is opioid analgesic tolerance? When does it start?
- What is opioid-induced hyperalgesia?