

# Turning the Tide of Chronic Opioid Therapy

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## DISCLOSURE & ACCREDITATION

**I have no conflicts of interest related to the content of this presentation.**



# Outline

- Chronic pain: pathophysiology and epidemiology
- Opioids:
  - Pharmacology, role in chronic non-cancer pain
  - Evidence base
  - Prescribing trends
- Guidelines in chronic opioid therapy
- Next steps aimed at improving quality of care

## Case #1

**29-year-old man** with recent back surgery for large intervertebral disk herniation referred for evaluation of possible opioid use disorder/addiction.

**CC:** ongoing sciatica, low back pain.

**PMHx:** PTSD

### **Pertinent data:**

- Morphine SA 30 mg TID with oxycodone IR 5-10 mg q4 hours; run out early twice
- Non adherent to sertraline, mental health appointments
- Sedentary but intermittent high intensity activity

**ROS:** Insomnia, nightmares, agitation, inability to sit through classes, considering withdrawal from school

## Case #2

**70-year-old man** with severe spinal stenosis, b/l hip/knee osteoarthritis referred for 2<sup>nd</sup> opinion about opioid regimen

**CC:** increasing frequency of low back pain paroxysms

**PMHx:** COPD, OSA on CPAP, obesity

### **Pertinent data:**

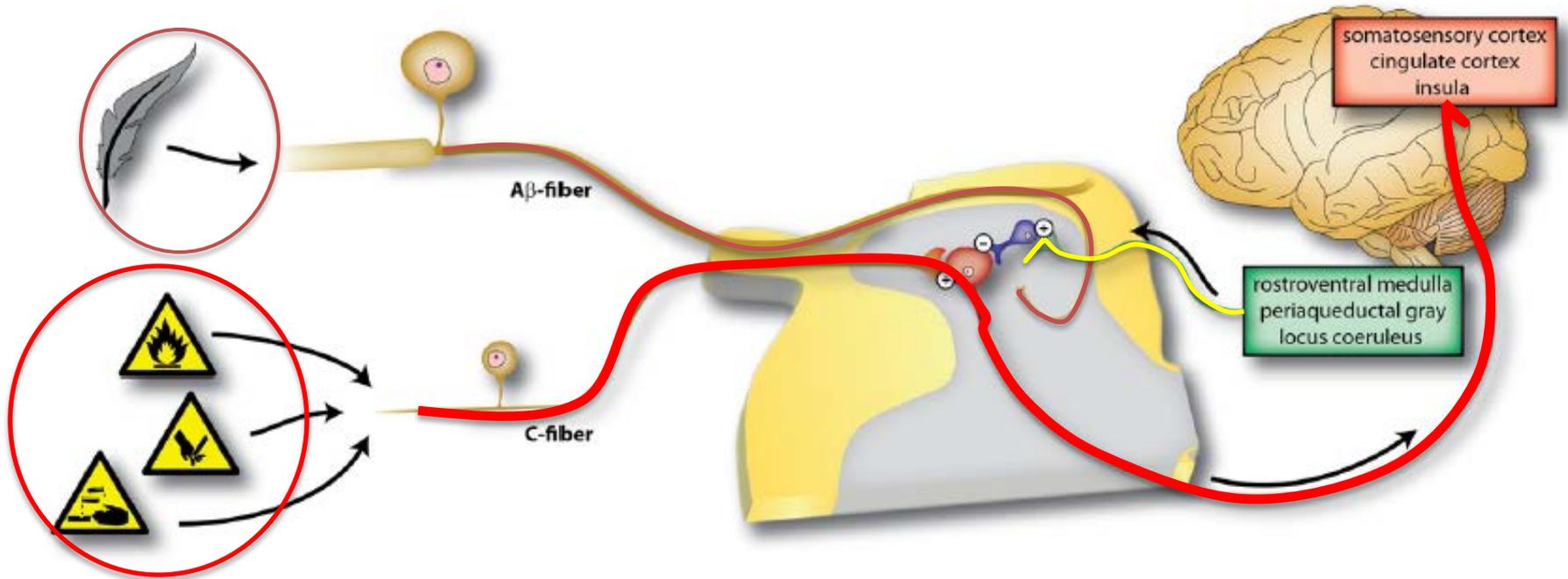
- Oxycodone IR 10 mg four times a day for 3 years
- Requests a dose increase
- Lives independently, active socially in the Elks and the Moose clubs. Collects hats, enjoys traditional Hungarian dance but currently slowed by pain.

PCP worried about potential consequences of dose escalation; wonders if long-acting agents would be more appropriate.

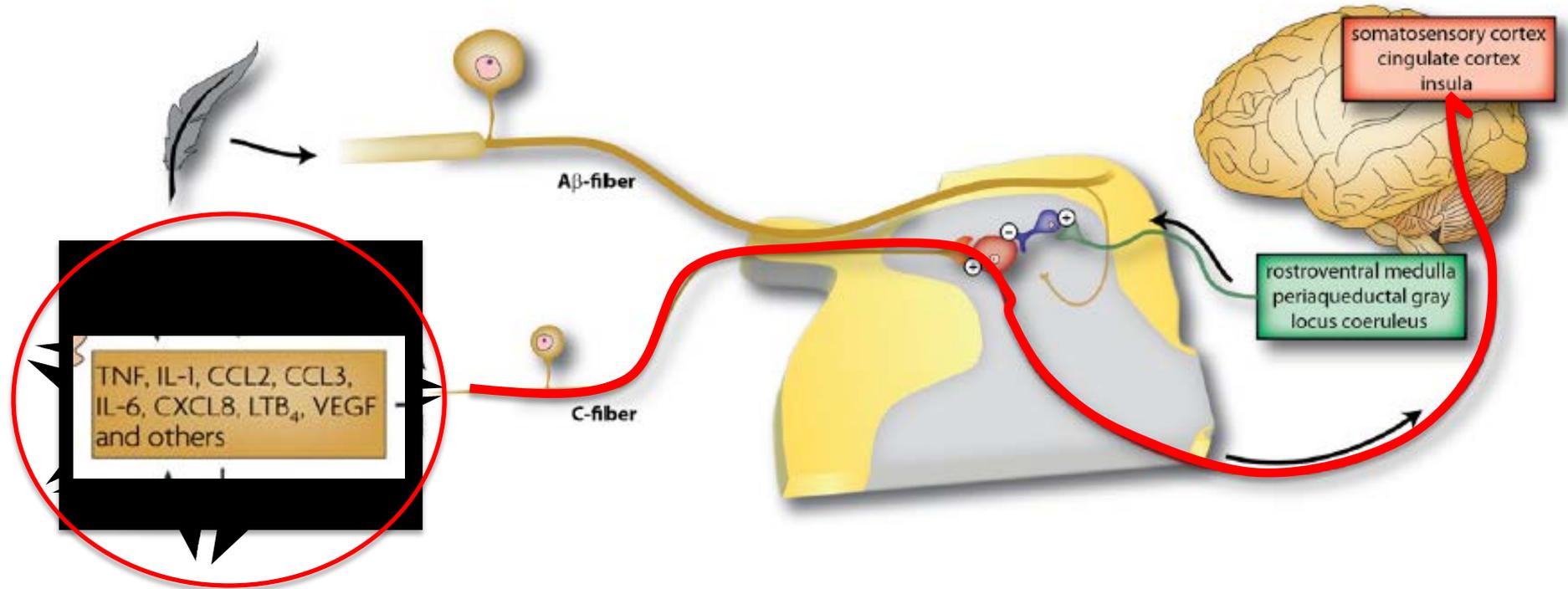
# Outline

- **Chronic pain: pathophysiology and epidemiology**
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# Acute pain



# Chronic inflammatory pain



# Chronic pain: neuronal plasticity and central sensitization

## Neuronal plasticity

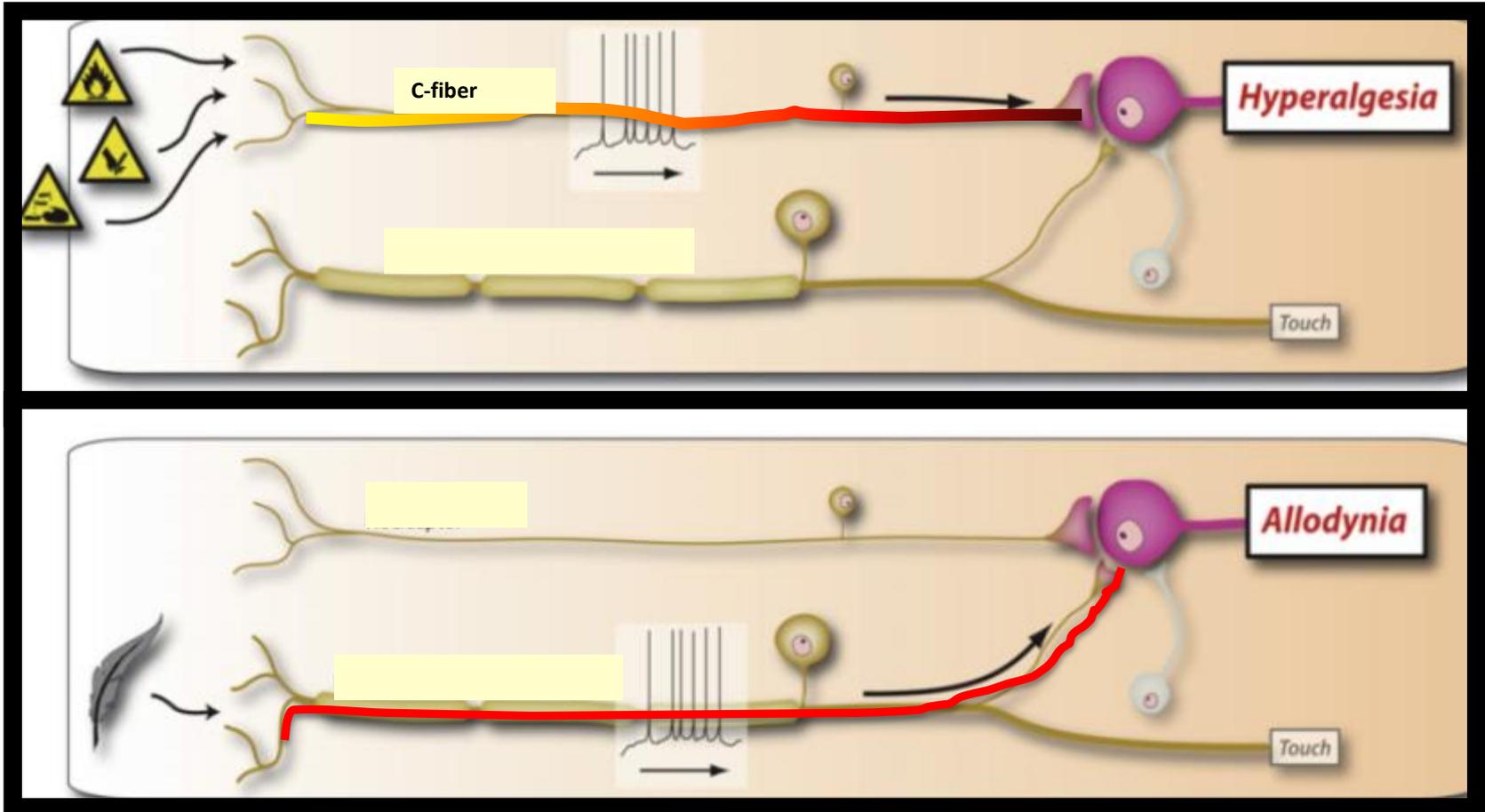
Peripheral nerve injury → recruitment of macrophages and glial cells → dysregulated nerve regeneration of both AB and c-fibers

## ↓ Central sensitization

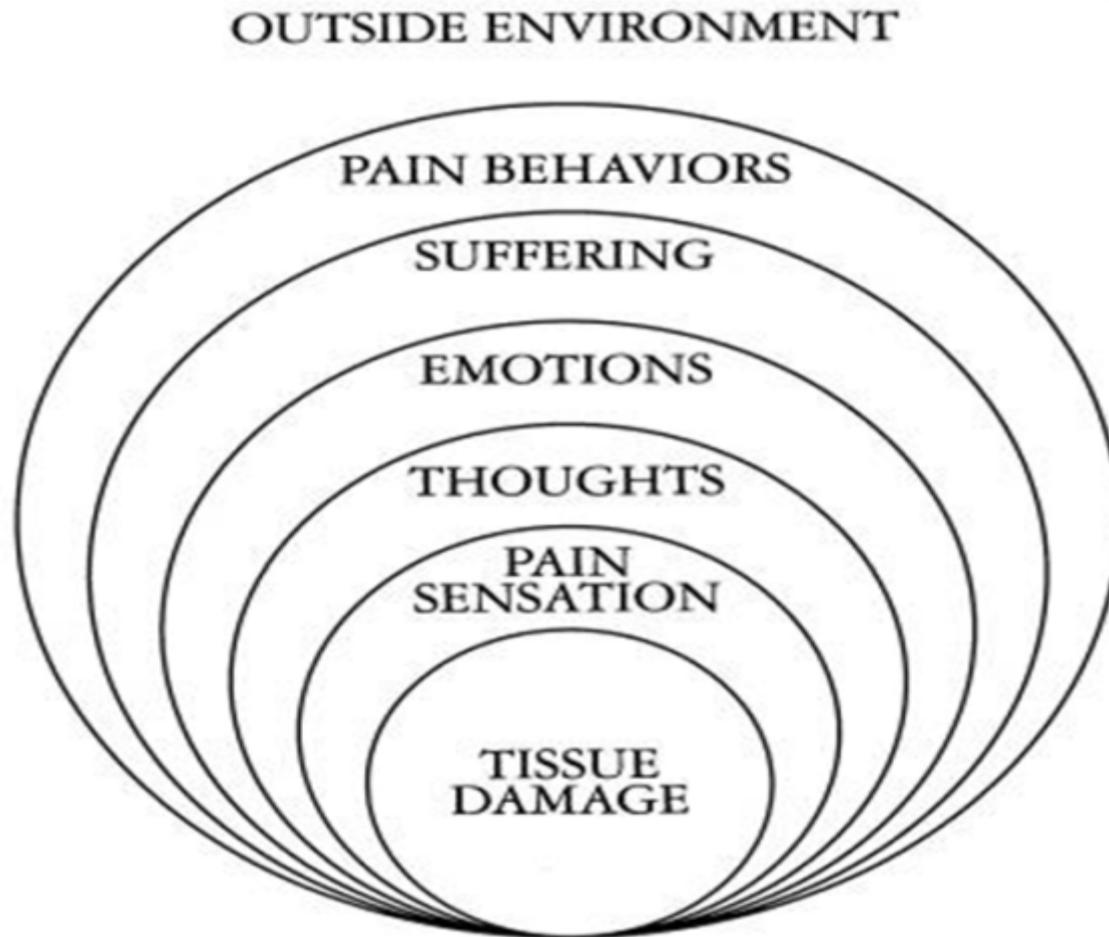
Excess of AB and c-fibers in dorsal horn → compensatory changes to NMDA receptors → lowered pain thresholds



# Chronic pain: hyperalgesia and allodynia

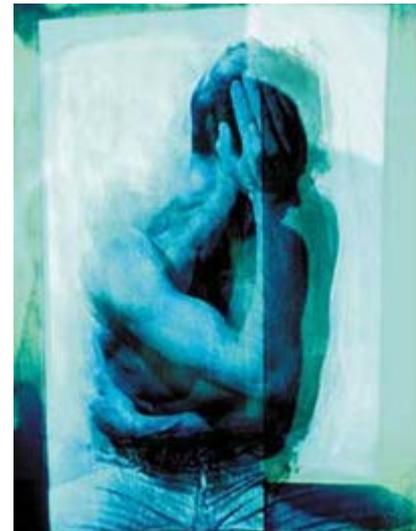


# Complexity of chronic pain



# Chronic pain: ubiquitous and costly

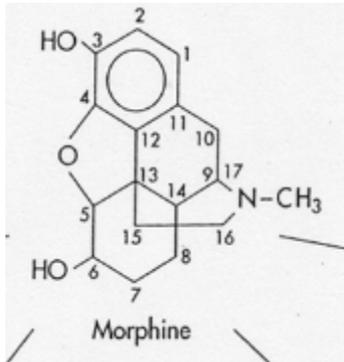
- Point prevalence: 25% in U.S. adults; 10% with disabling chronic pain that limits work and family activity
- Second most common reason for outpatient visits
- Annual national economic cost estimated up to \$635 billion
- 2011: Five of U.S.' 133 medical schools had mandatory course on pain



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# Opioid analgesics (opiates + opioids)

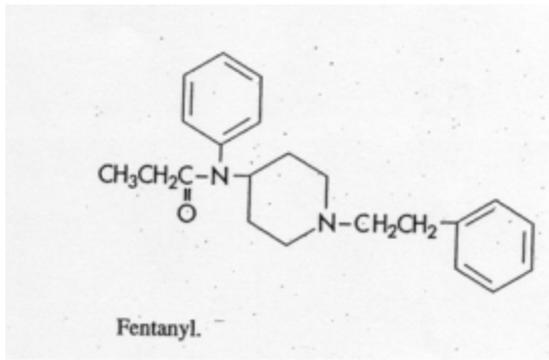


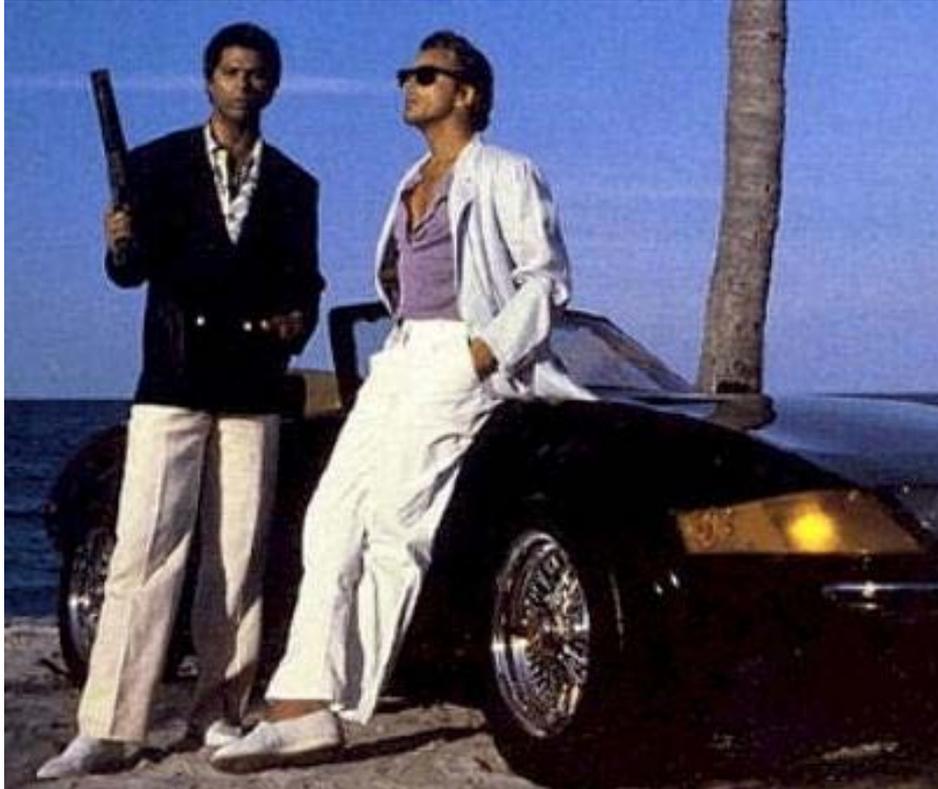
## Opiates

- Naturally present in opium from seedpod of *Papaver somniferum*
- Morphine, codeine

## Opioids

- Manufactured
- Semi-synthetics: hydrocodone, hydromorphone
- Synthetics: fentanyl, methadone





# Morphine equivalent dose

- Method of standardizing potency across various opioid compounds
- Based on equianalgesic tables from dose ranging studies

- Example:

20 mg oxycodone TID

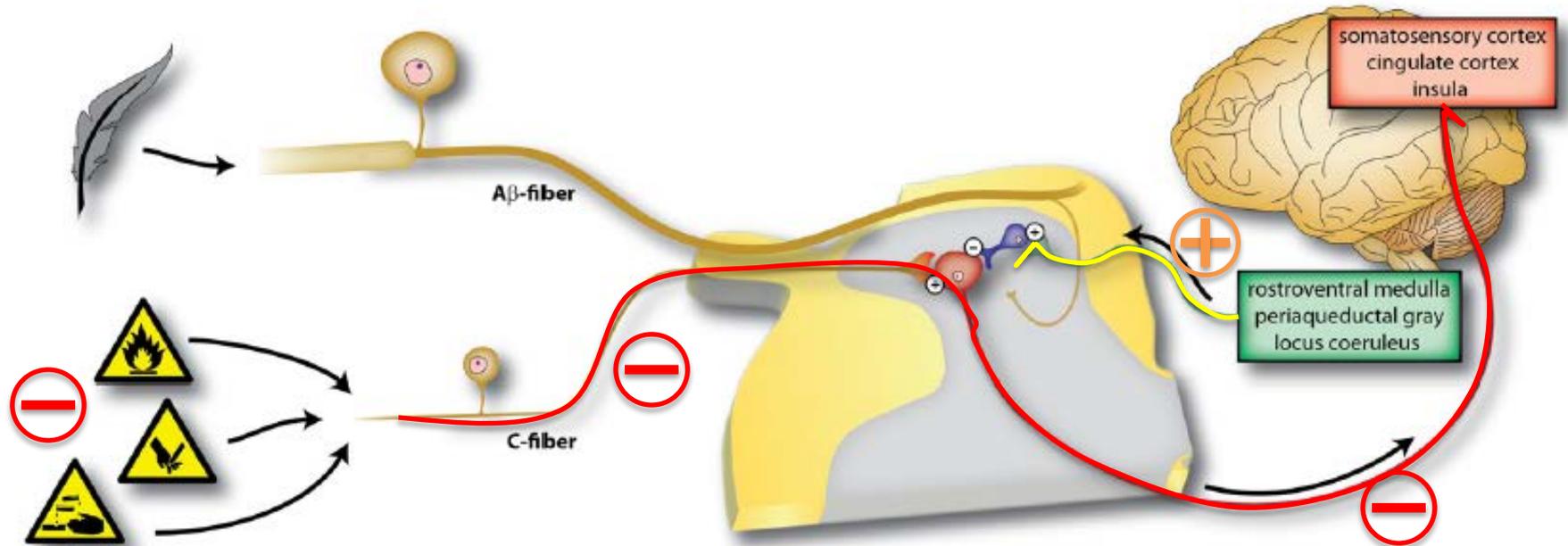
=

90 mg morphine

equivalent daily dose

<b>Equianalgesic dose (MG)</b>	<b>Opioid (oral)</b>
<b>30</b>	<b>Morphine</b>
<b>7.5</b>	<b>Hydromorphone</b>
<b>20</b>	<b>Oxycodone</b>
<b>30</b>	<b>Hydrocodone</b>

# Activation of mu receptors



# Opioids: undisputed indication



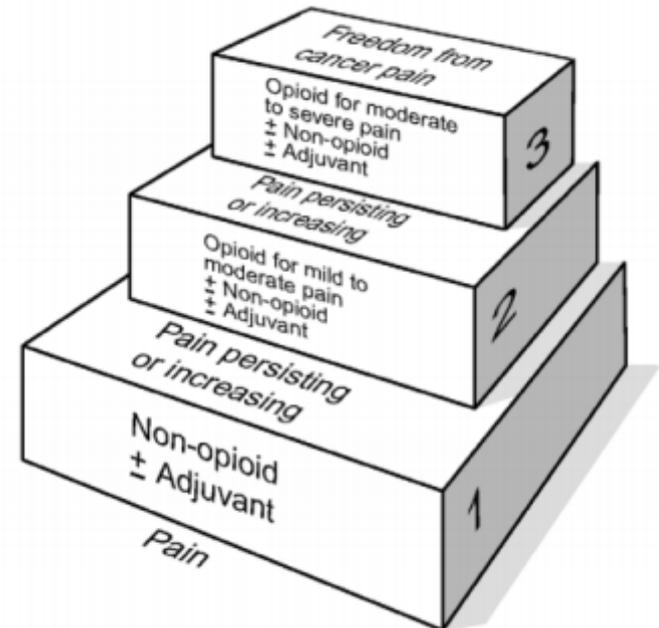
## SUBCUTANEOUS INJECTIONS OF MORPHINE FOR WOUNDED MEN.

*To the Editors of THE LANCET.*

SIRS, — The utility of morphine injections in saving suffering during the removal of wounded men seems so obvious that you may think it unnecessary to insert this letter, ... (T. Lauder Brunton, 1899)

Acute pain

End-of-life related pain



# Opioids & chronic non-cancer pain

# Sequelae of long-term opioids

**Tolerance** → higher doses required to achieve same analgesic effect over time

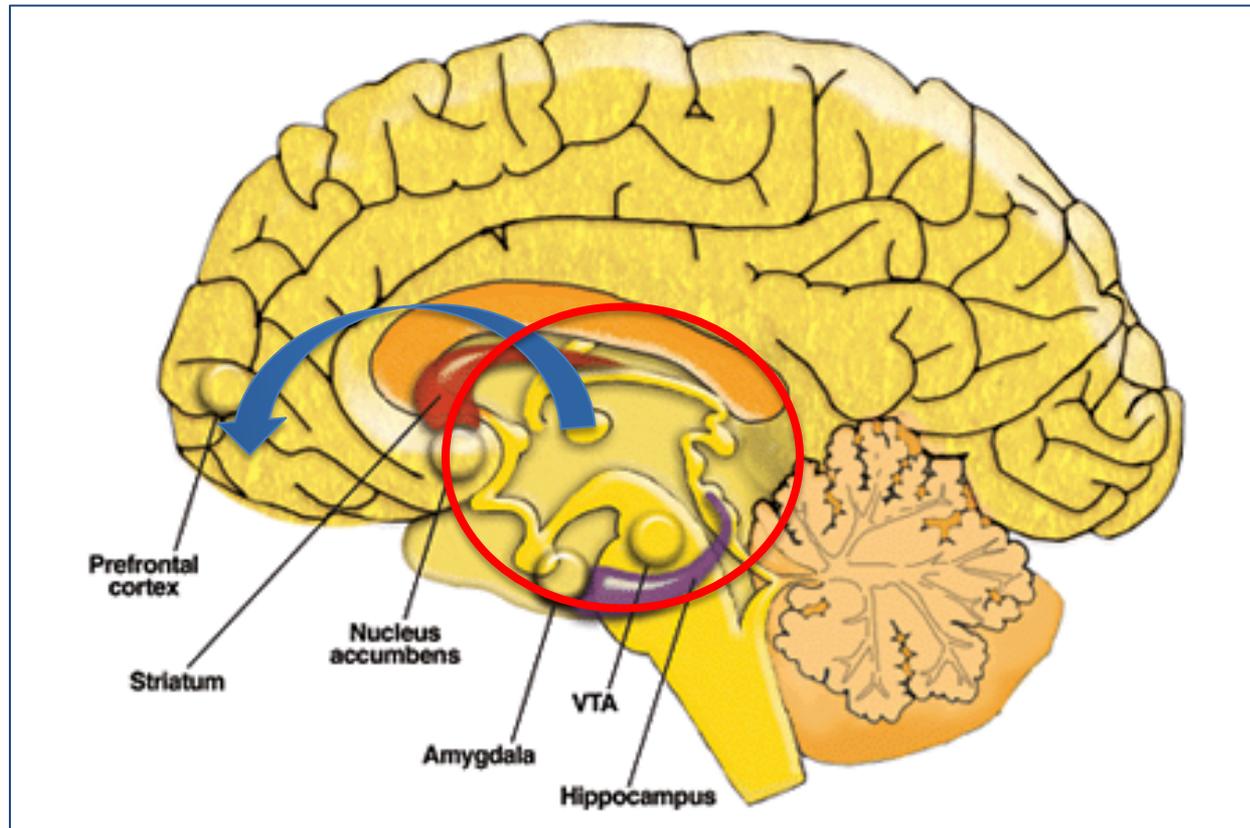
- High prevalence
- Also develops to some of the toxic effects

**Withdrawal** → characteristic symptoms upon abrupt cessation or lowering of opioid dose

**Opioid-induced hyperalgesia** → paradoxical worsening of pain with higher doses

- Prevalence unknown
- Correlation with total opioid exposure (dose x time)

# Mu receptors and reward pathways



# Opioid use disorder (DSM-V)

## Physiologic sequelae

- Tolerance
- Withdrawal
- Opioid craving

## Loss of control

- Greater amounts of use or longer period of use than intended
- Persistent desire but unsuccessful efforts to cut down
- Inordinate amount of time obtaining, using, or recovering

## Adverse consequences

Summary of 5 criteria:

- Important social, occupational or recreational activities given up or reduced due to opioid use or recurrent opioid use despite physical or psychological problems caused or worsened by use

# Other important toxicities

- Constipation
- Itching
- Nausea/vomiting
- Hypogonadism
- Opioid-induced hyperalgesia
- Sedation
- Impaired cognition
- Falls/motor vehicle accidents
- Blunted respiratory drive
- ***Non-fatal and fatal overdose***

# Odds of overdose by increasing dose

	Dunn	Gomes	Bohnert
Dose* (mg/day)	HR (95% CI)	OR (95% CI)	HR (95% CI)
1-<20	1.00 (REF)	1.00 (REF)	1.00 (REF)
20-<50	1.2 (0.4-3.6)	1.3 (0.9-1.8)	<b>1.9 (1.3-2.7)</b>
50-<100	<b>3.1 (1.0-9.5)</b>	<b>1.9 (1.3-2.9)</b>	<b>4.6 (3.2-6.7)</b>
≥100 or 100-199	<b>11.2 (4.8-26.0)</b>	<b>2.0 (1.3-3.2)</b>	<b>7.2 (4.9-10.7)</b>
≥200		<b>2.9 (1.8-4.6)</b>	

\*morphine equivalent

Dunn et al. Annals IM 2010; Gomes et al. Archives IM 2011; Bohnert et al. JAMA 2011

Slide courtesy of JW Frank, MD, MPH

# Opioids for chronic pain: important limitations

- Central sensitization may not be responsive to opioids
- Chronic pain has prominent psychological component; unclear role for opioids
- Long term therapy induces tolerance, necessitating higher doses
- Higher doses chronically → increased risk of opioid-induced hyperalgesia
- Higher doses → increased risk of toxicity, both acute and chronic

Evidence base: opioids for chronic  
non-cancer pain

# Opioids for chronic low back pain

Figure 2. Results of meta-analysis of opioid efficacy with nonopioids or placebo comparisons

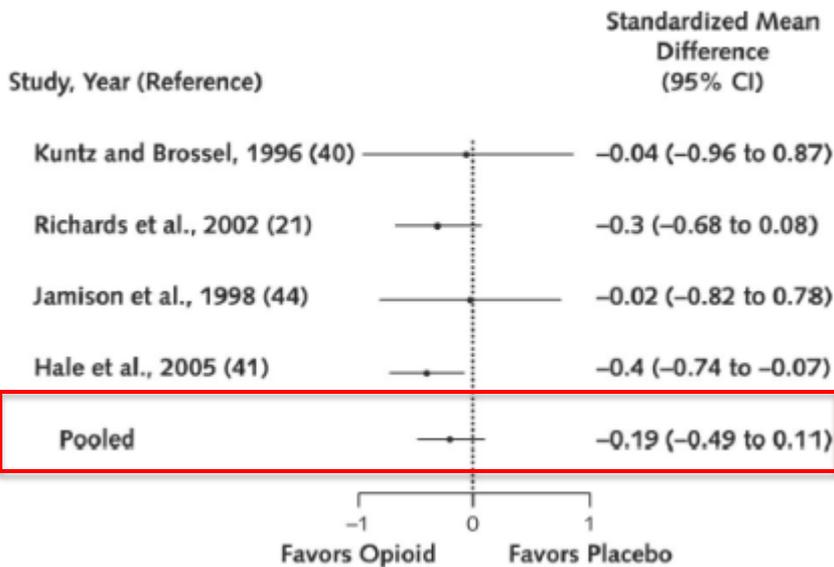
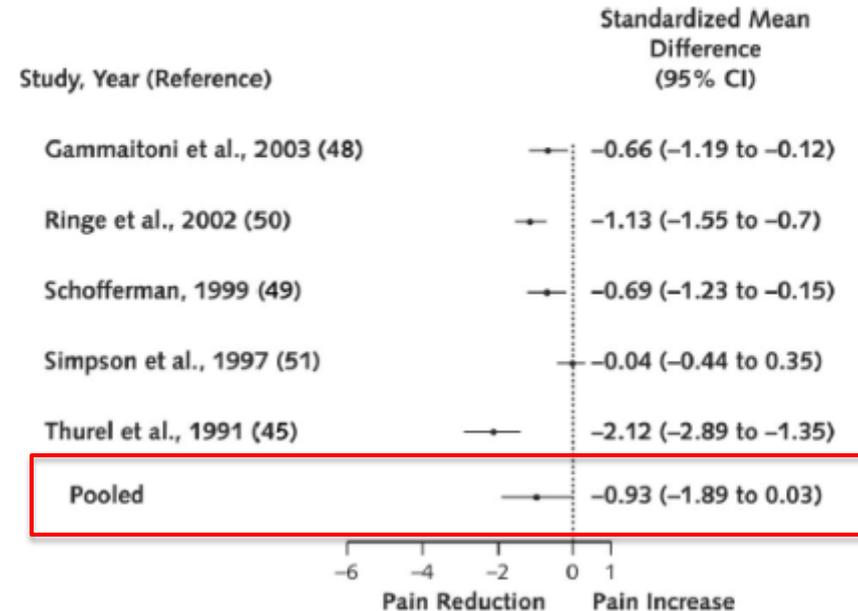


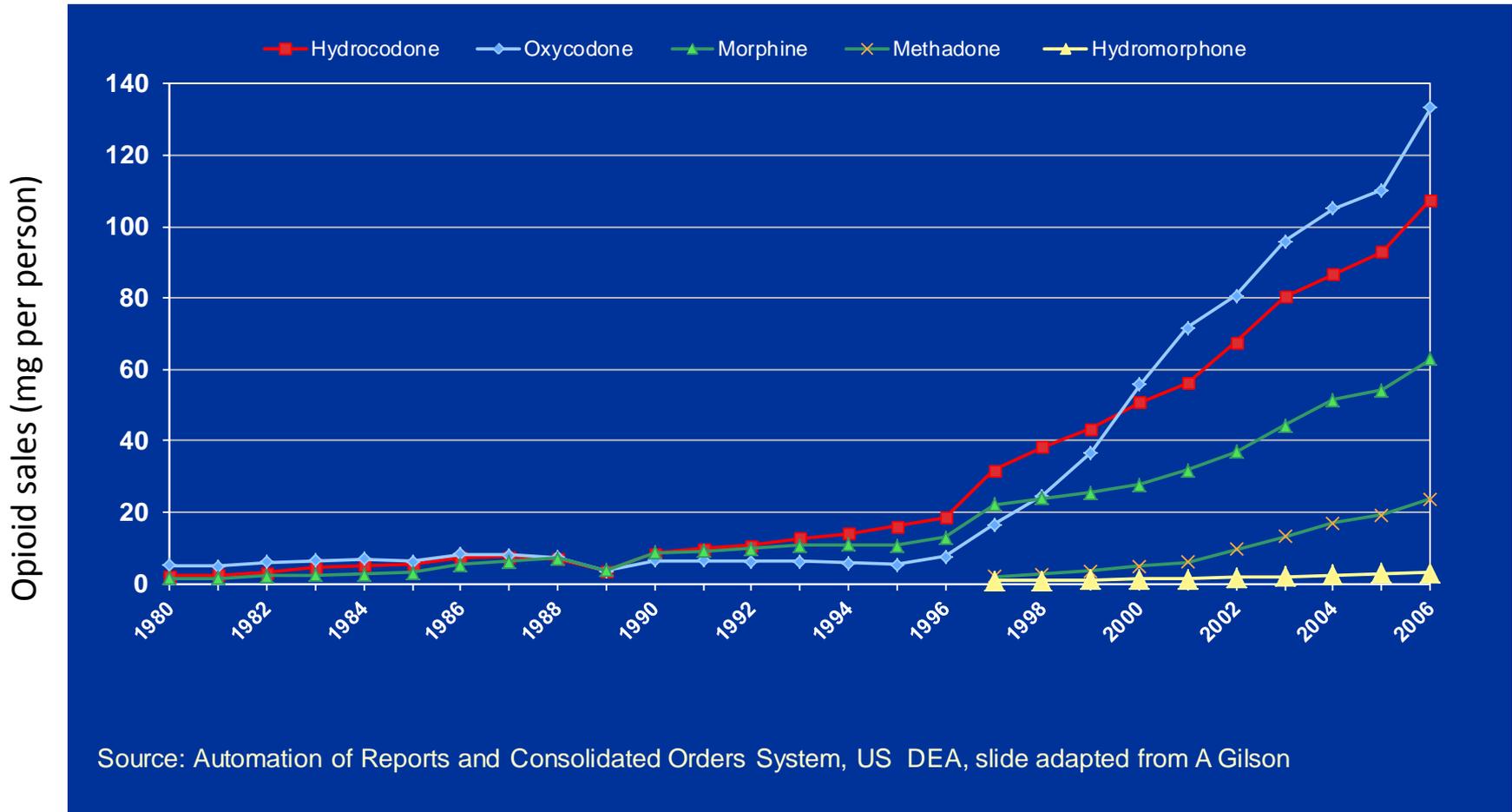
Figure 3. Results of meta-analysis of opioid efficacy with opioid comparisons



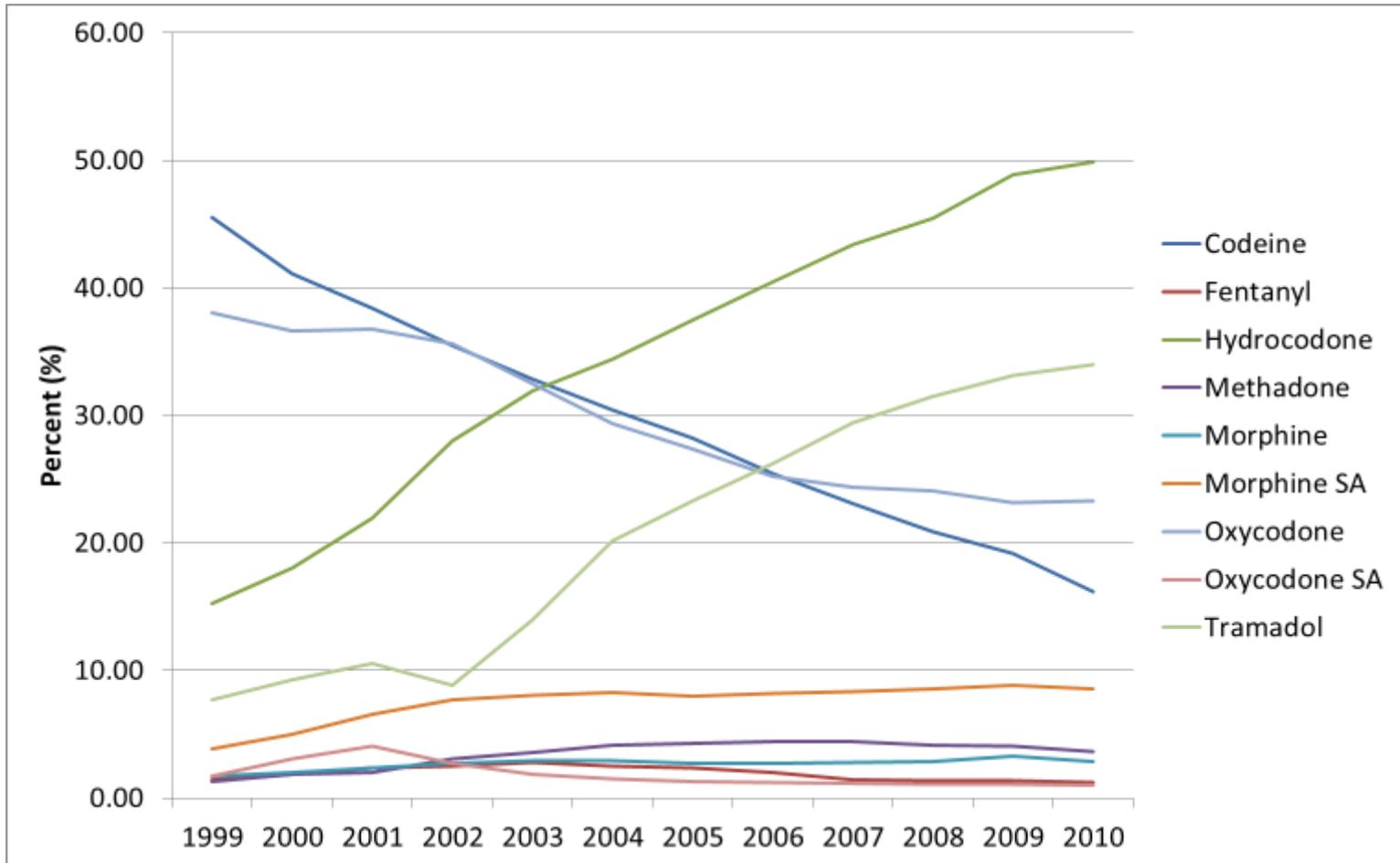
# Evidence for long-term use

- RCTs, non-randomized trials, pre-post case series, variety of pain conditions examining outcomes  $\geq 6$  months:
- “Despite the identification of 26 treatment groups with 4768 participants, the evidence regarding the effectiveness of long-term opioid therapy in chronic non-cancer pain is too sparse to draw firm conclusions...”
- Medium effect size in study completers, but they were small proportion of sample
- No long-term studies included functional outcomes

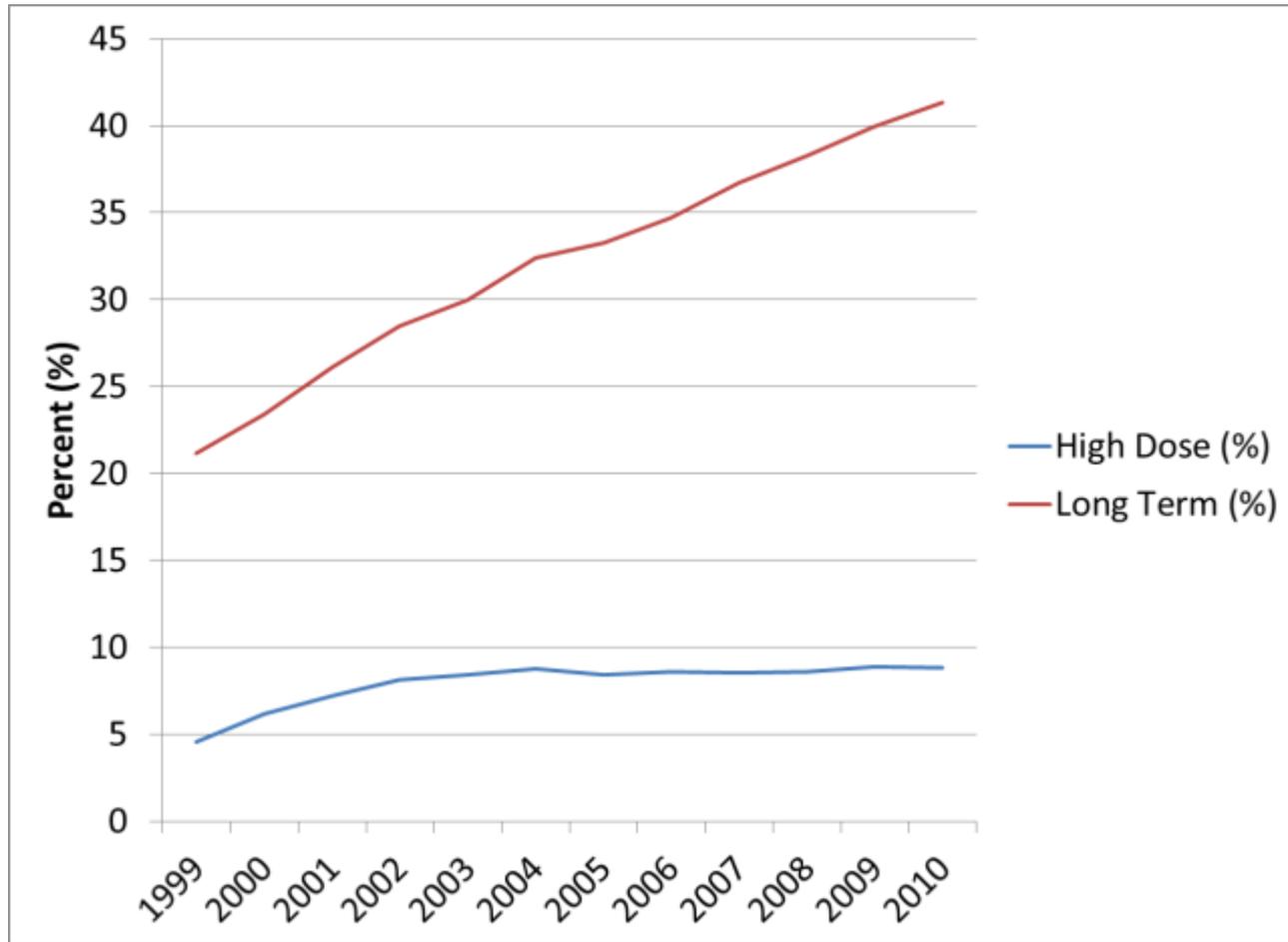
# Increase in opioid prescription



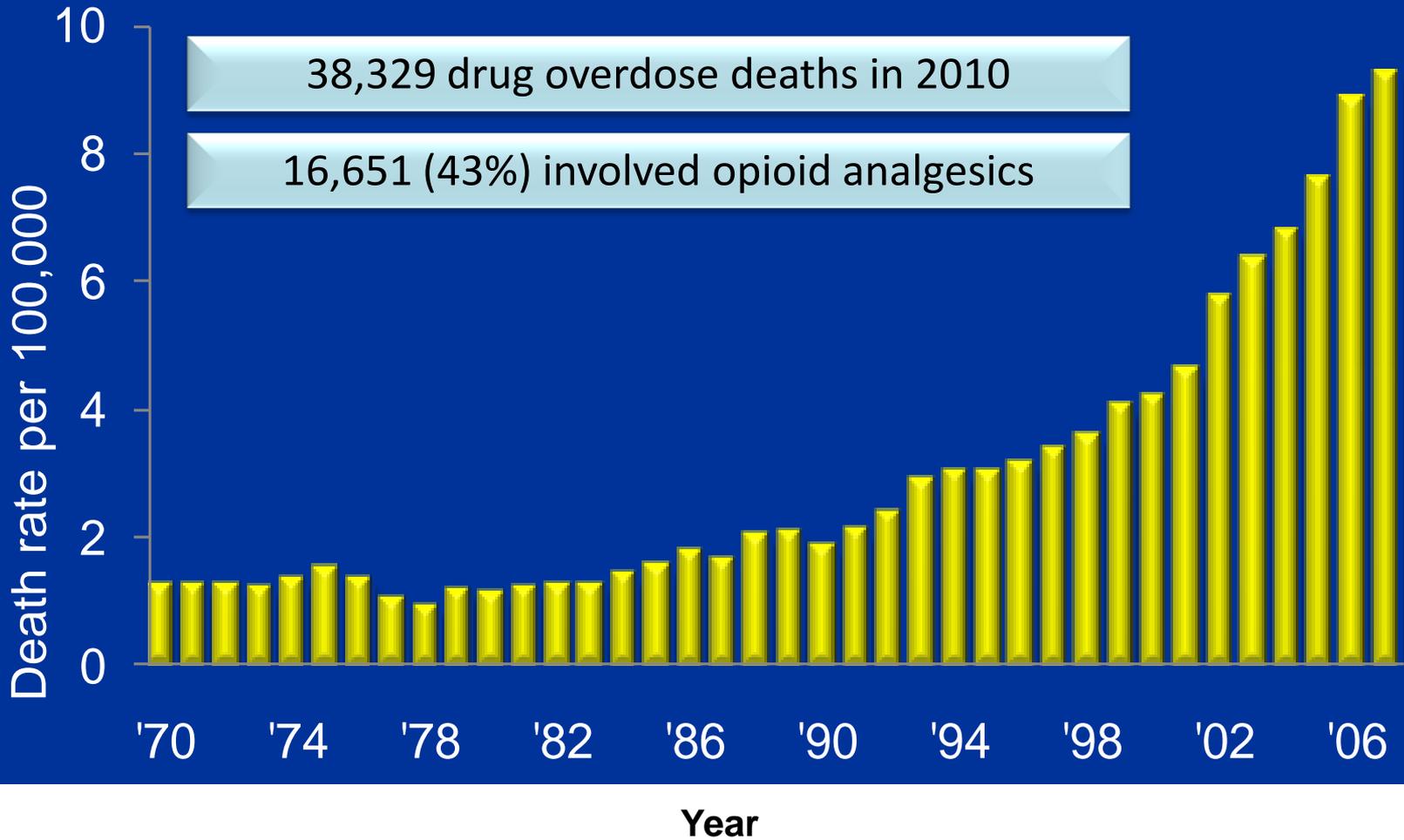
# Similar trends in VA



# Increases in high-dose and long-term prescribing



# Trends in opioid overdose death



# How did we get here?

- **Public health campaigns against pain**



- **Aggressive & sometimes deceptive marketing**
  - Extrapolation from cancer/acute pain data
  - Purdue pharma officials found guilty of misbranding; fined \$600 million
- **Clinical inertia**

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ELSEVIER

# Opioid Treatment Guidelines

## Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

### Key summary points:

- “Clinicians may consider a trial of chronic opioid therapy if chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).”
- Multi-modal care
- Structured monitoring: *Continue if safe and effective, discontinue if unsafe or ineffective*

# Gaps in the guidelines

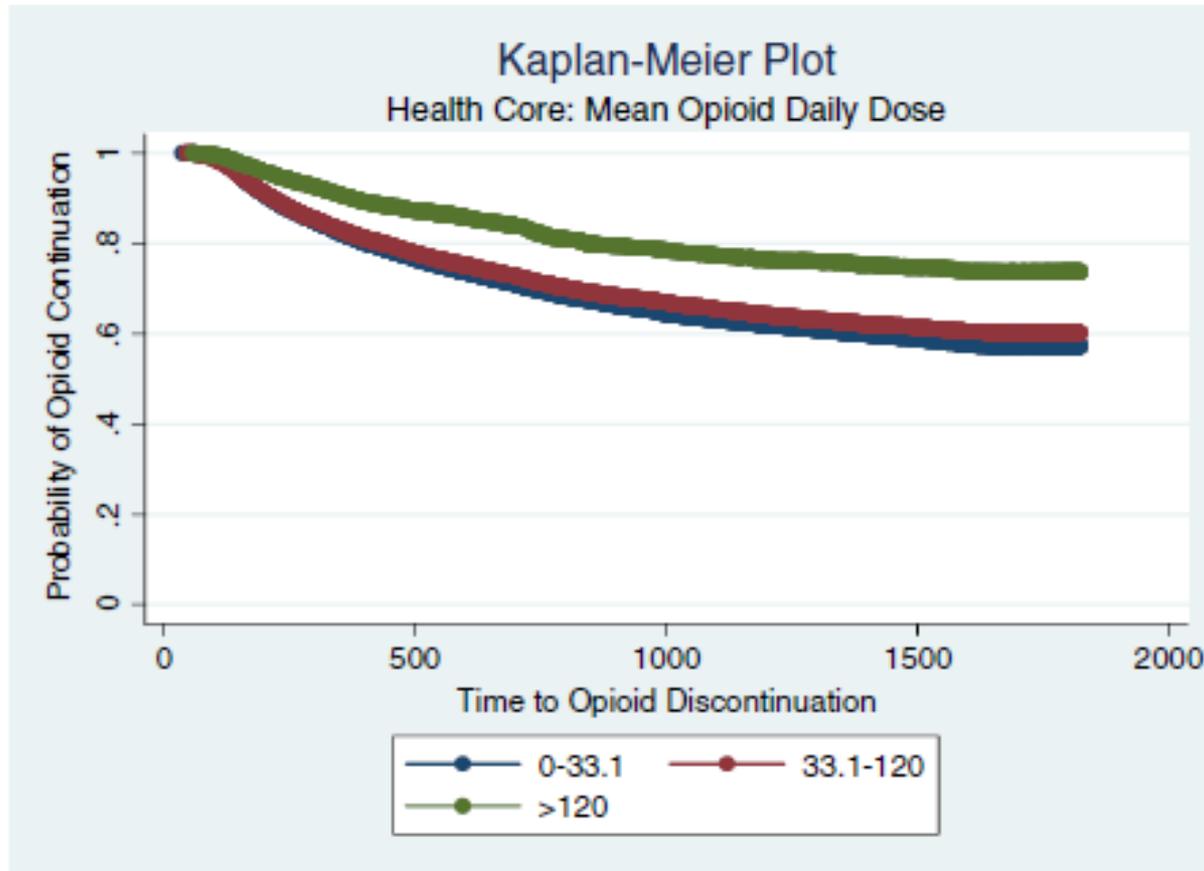
- How do we systematically assess harm and benefit?
- What do we do once harm or absence of benefit is identified?
  - Discontinuation protocols
  - Alternative treatment options
- What about dose?

# Monitoring is lax

In a cohort of 1600+ patients on long-term opioids in primary care followed for up to 4 years:

- 7% → at least one urine drug test
- 49% → regular office visits
- 74% → limited early refills

# Opioid discontinuation is rare



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# **Transforming VA Pain Care**

## ***The Six Essential Elements of Good Pain Care***

- 1. Educate Veterans/families to promote self-efficacy and shared decision making; provide access to relevant resources**
- 2. Educate/train all team members to discipline specific competencies, including team based care**
- 3. Develop and integrate non-pharmacological modalities into care plans**
- 4. Institute rational medication prescribing, use of pain procedures and safe opioid use**
- 5. Implement approaches for bringing the Veteran's whole team together and for maintaining ongoing communication**
- 6. Establish metrics to monitor pain care and outcomes at both the individual level and the population level**

# Clinical research agenda

- How do we systematically assess harm and benefit?  
**Develop an easy-to-use monitoring algorithm**
- What do we do once harm or absence of benefit is identified?  
**Design and test alternative treatment strategies**
- What about dose?  
**Inform guidelines on dose and duration limits**

# Develop an easy-to-use monitoring algorithm

- Starting point: brief patient-reported checklist assessing opioid safety, efficacy, misuse
- Universal use of treatment agreements
- Routine access to prescription monitoring programs
- Routine, judicious use of urine drug testing

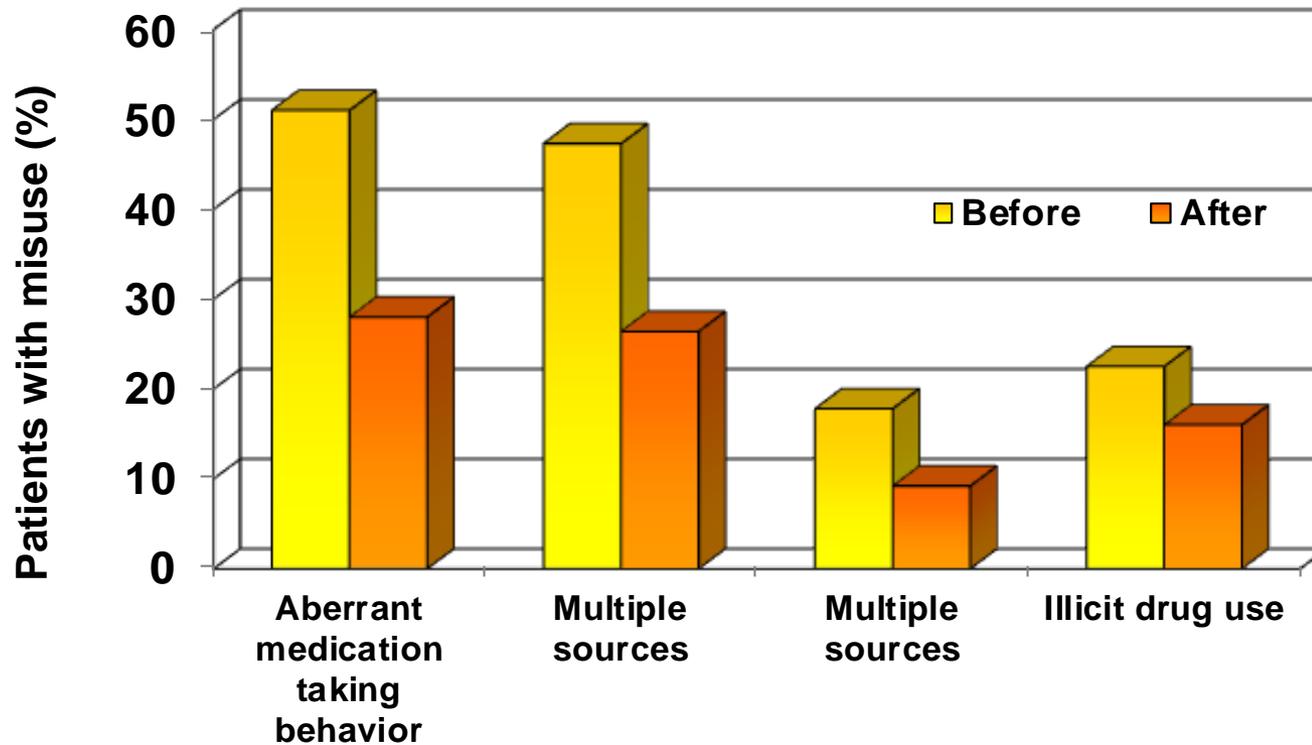
# Brief checklist development

- Systematic review of other instruments:
  - Too long, lacked safety/efficacy items
  - Not validated in actual clinical care
- Safety, efficacy, misuse of opioids; 10 items or fewer
- Patient self-report, self-administered
- Every patient, every visit and perhaps between visits
- Any item endorsed should prompt clinician follow-up

# Opioid treatment agreement

- Written document outlining goals of therapy, plan of care, and expectations for safe opioid use
- Goals: focus on function→
  - Specific
  - Measurable
  - Action-oriented
  - Realistic
  - Timebound
- Frequently revisited
- When necessary, cite as evidence that harm is outweighing benefit of therapy

# Treatment agreements reduce opioid misuse



# Prescription drug monitoring program (PDMP)

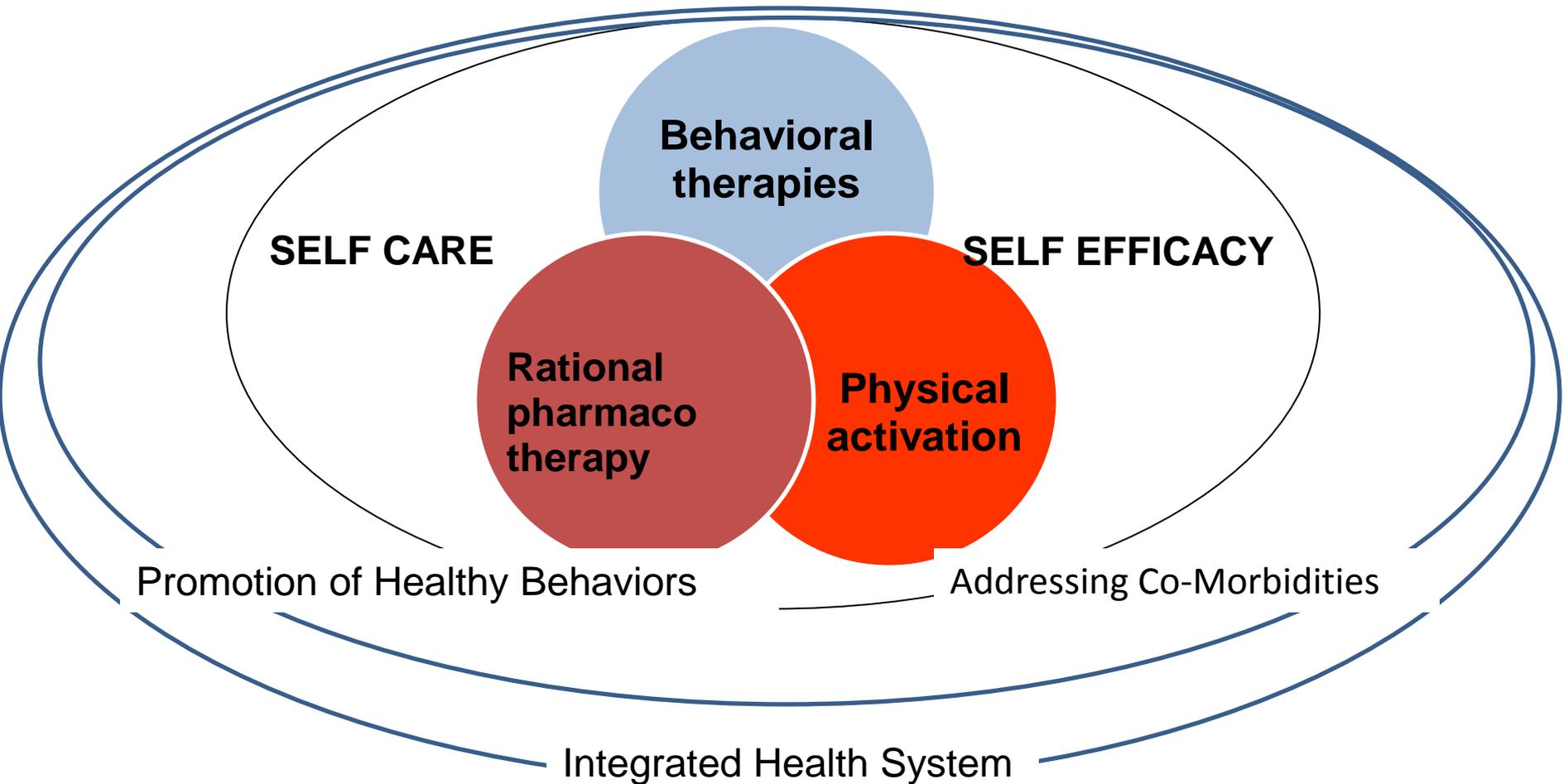
- Listing of all controlled substances filled by patient in the state; pharmacy reporting is state law
- Allows prescribers to track multiple fills or “doctor shopping”
- Need a DEA# to register
- Can also query yourself (as prescriber)
- Population-level data equivocal on benefit
- Prescriber level qualitative data → increased provider comfort and confidence

# Have an exit strategy

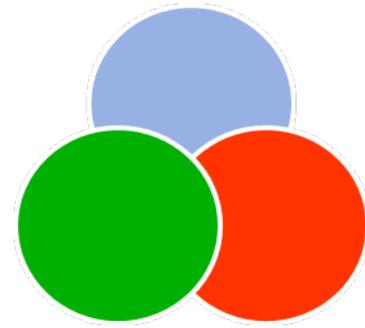
- Treatment agreement:
  - Duration of therapy and discontinuation plan
  - Plan regarding dose
  - What will happen if opioids are not effective
  - What will happen if treatment agreement is not followed (e.g. taper, immediate discontinuation, transition to alternative treatments)

# Design and test alternative treatment strategies

# IOM's vision for multimodal chronic pain care



# Evidence-based non-pharmacologic treatments for chronic pain



## Physical activation

- Low intensity aerobic exercise
- Physical therapy
- Yoga
- Tai Chi
- Aquatherapy

## Behavioral treatments

- Cognitive behavioral therapy
- Mindfulness/meditation
- Progressive muscle relaxation

- Biofeedback

## Other techniques

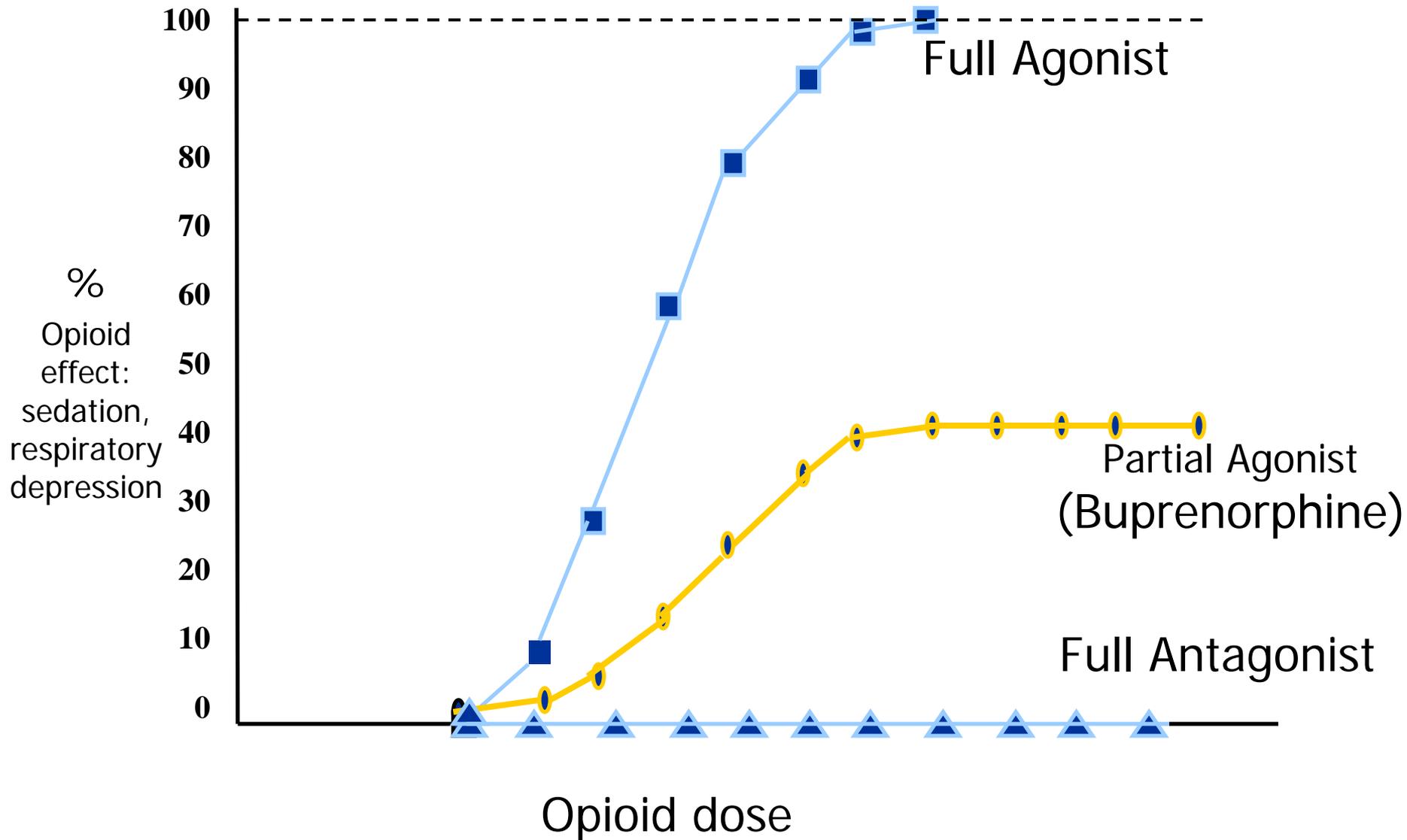
- Massage
- Chiropractic
- Acupuncture
- Trigger point injections
- Botox injections
- Intra-articular steroid injection
- TENS
- Nerve blocks

# Making “multi-modal” a reality

- Integrated Pain Clinic: 2-hour, multi-disciplinary pain assessment (Health Psychology, Pain Medicine, Physiatry, Physical Therapy)
- Opioid Reassessment Clinic: longitudinal multi-disciplinary assessment and treatment (Addiction Psychiatry, Health Psychology, Internal Medicine)
- Educational programming for PCPs: how to communicate and enhance motivation for multi-modal care

# Novel pharmacotherapies

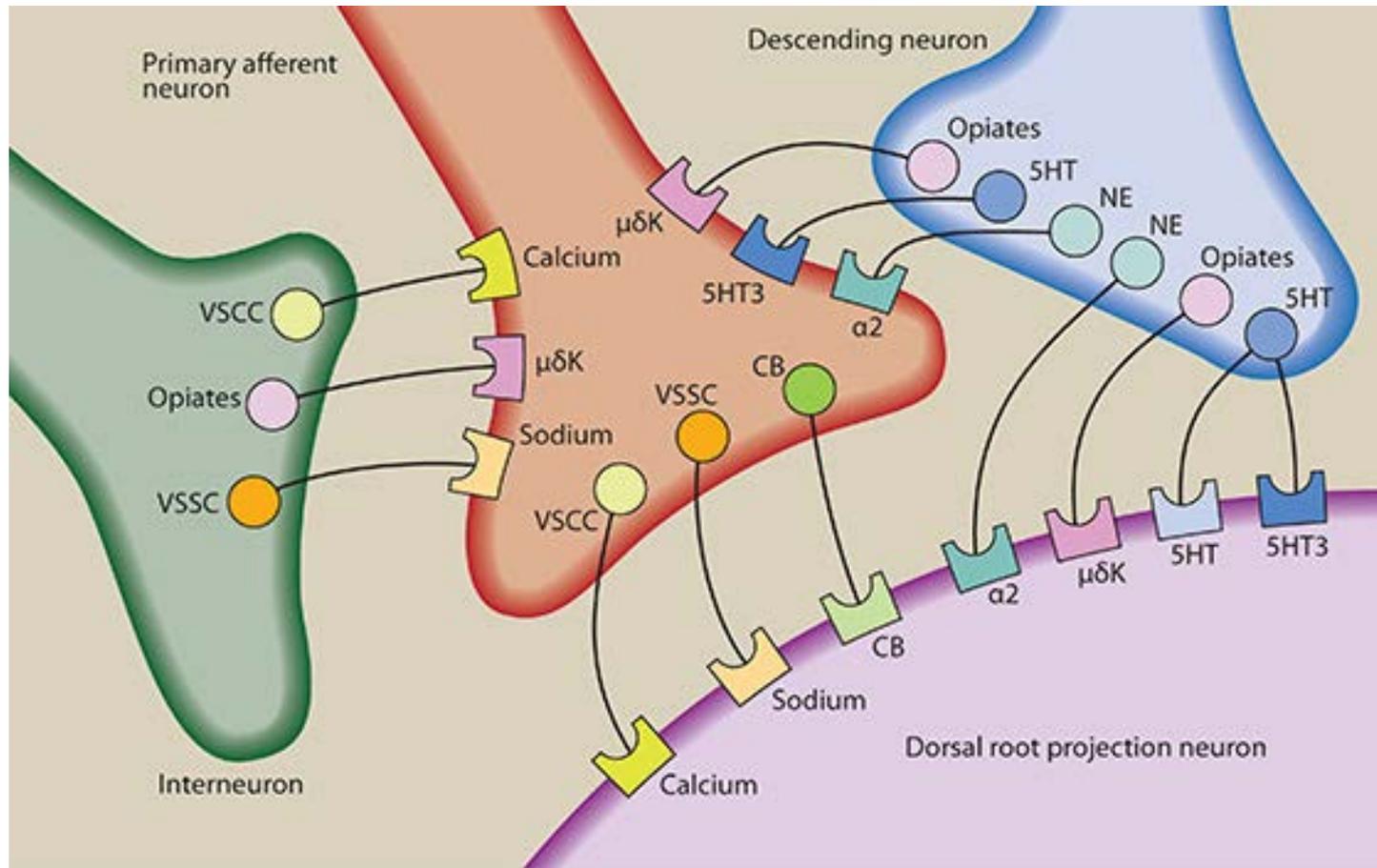
# Buprenorphine: a partial mu agonist



# Potential roles for buprenorphine

- First-line therapy for chronic non-cancer pain
- Assist with transition off of full agonist opioids when:
  - Maximum duration reached
  - Full agonists ineffective
  - Intolerable side effects (e.g. over sedation)

# SNRIs, gabapentanoids, ?cannabinoids



# Dose and adverse events

# Veterans Aging Cohort Study



- Prospective, observational cohort study of HIV(+) and demographically matched HIV(-) veterans in the US
- Examines role of comorbid disease in determining clinical outcomes in HIV infection
- Harnesses robust VA electronic health record: laboratory, pharmacy, diagnostic data over 14 years
- Opioids Workgroup



# Opioids workgroup analyses

- Demographic and clinical correlates of any, high dose, long term opioid receipt (Edelman et al, JGIM 2012)
- 12-year trends analysis
- Next steps:
  - Opioids and polypharmacy (D. Weisberg)
  - Association between opioid dose and important adverse effects:
    - Falls, fractures
    - Sleep-disordered breathing
    - Non fatal, fatal overdose
  - Collaborating with VA national medication quality and safety office

Back to the cases...

## Case #1

**29-year-old man** 5 months after back surgery, chronic low-back pain on morphine long-acting with oxycodone for breakthrough; has run out early twice.

### Assessment:

- 1) Opioid use disorder: tolerance, withdrawal, craving, adverse consequences (withdrawal from school)
- 2) Poorly controlled pain and non-engagement with multimodal pain treatment plan

### Treatment recommendations/plan:

Transition to buprenorphine, SA counseling

Motivational enhancement to reengage with PTSD treatment and physical therapy.

Gabapentin added.

Vocational counseling; Case worker assigned.

## Case #2

**70-year-old man** with severe spinal stenosis, generalized osteoarthritis, on oxycodone 10 mg four times a day for 3 years; efficacy has waned.

### Assessment:

- 1) Opioid tolerance
- 2) Unable to achieve functional goals despite engagement in multimodal therapy

### Treatment recommendations:

10%-20% dose increase → still results in moderate dose therapy

Continue to encourage appropriate coping strategies

Avoid >20% dose increase and/or switch to long-acting formulation

# Summary

- Despite physiologic limitations and modest evidence of efficacy, opioid prescribing for chronic pain has skyrocketed.
- Guidelines regarding chronic opioid therapy may not curtail current trends.
- Improved monitoring tools, discontinuation protocols and alternative treatment strategies are needed to improve safety and efficacy of chronic pain treatment.
- Dose and duration limits are needed to decrease opioid exposure.

# Thank you

Robert Kerns

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Opioid Reassessment Clinic team @ VACHS

Integrated Pain Clinic team @ VACHS

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Nancy Wiedemer and Mac Gallagher of PVAMC

VA Painiacs