

Chronic pain and Mary Jane:

Are cannabinoids the “high”way to relief?



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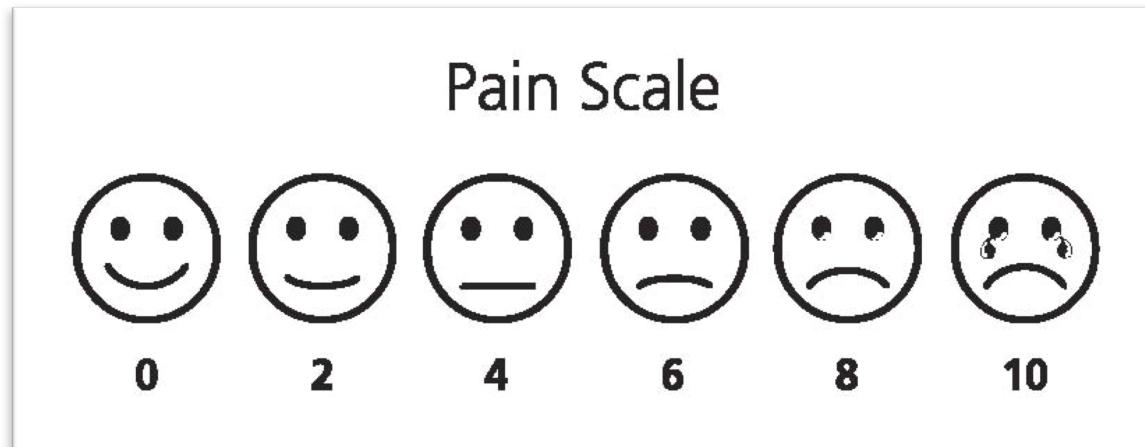
WASHINGTON STATE UNIVERSITY



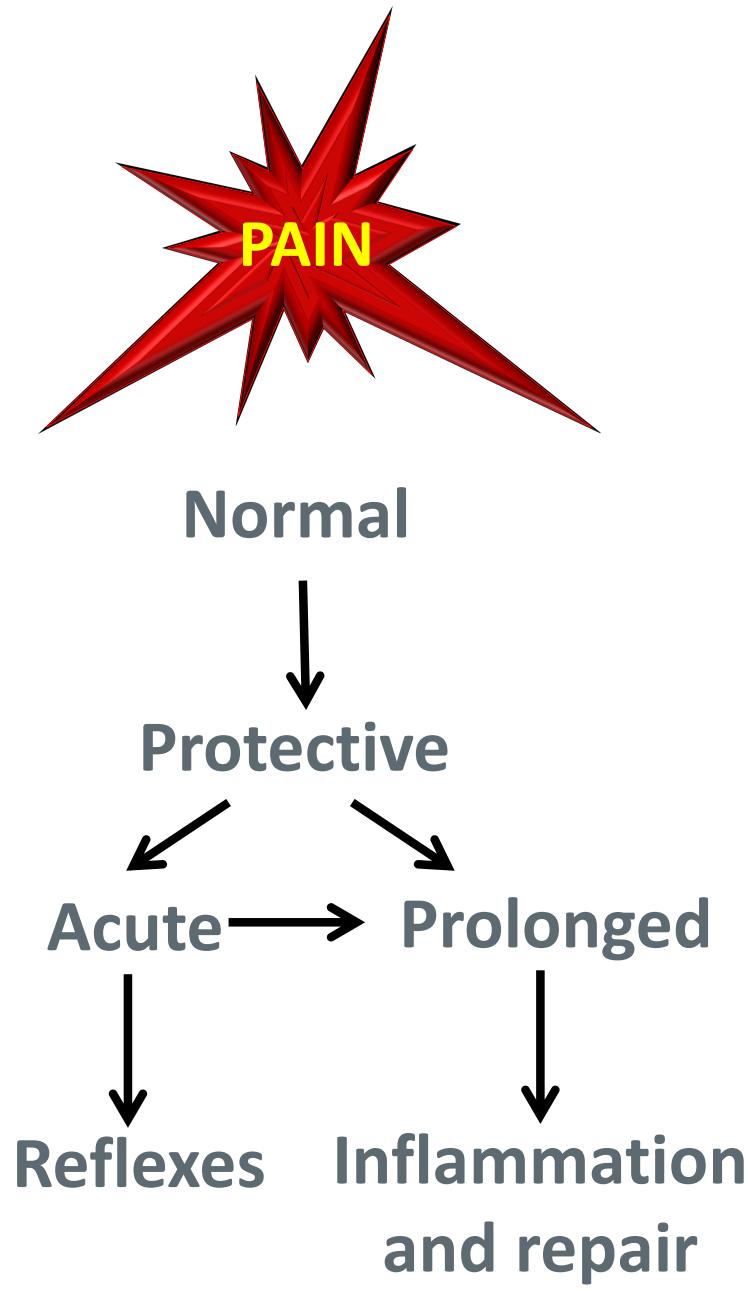
What is pain?

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

-International Association for the Study of Pain (IASP)



The two faces of pain: Protection and disease



Abnormal

↓

Non-protective

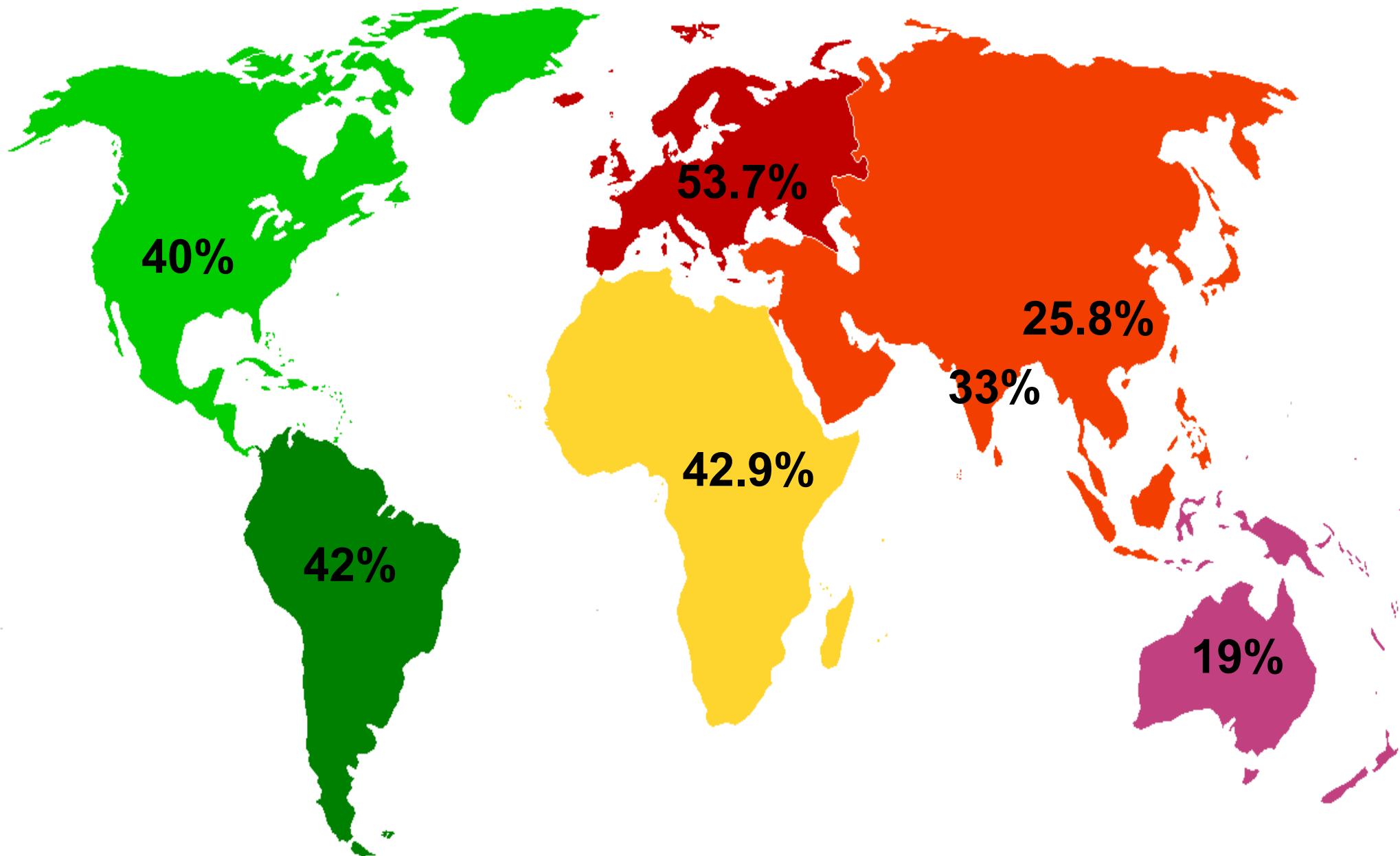
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Chronic (Pain as Disease)



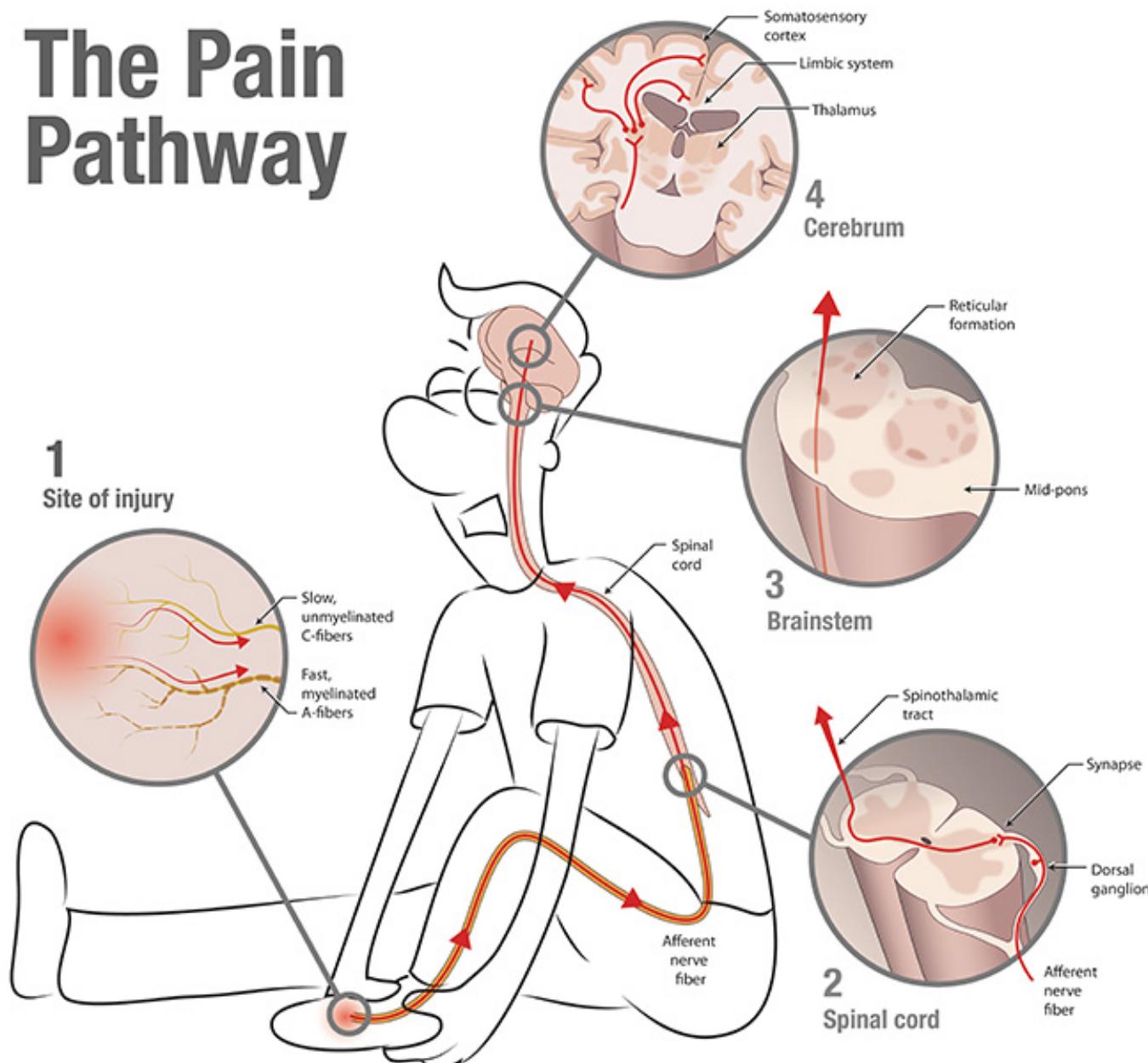
Therapeutic goal:
Eliminate abnormal pain
without interfering with normal,
protective pain

Chronic pain is a highly prevalent problem worldwide



The body interprets pain using a simple neural pathway

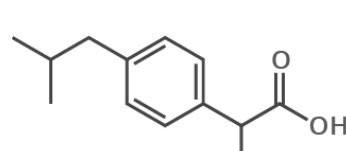
The Pain Pathway



Chronic pain is poorly treated

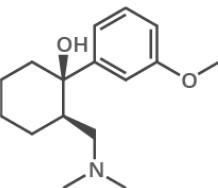
IBUPROFEN

POTENTIAL FOR SERIOUS SIDE EFFECTS LESS THAN OTHER NSAIDS



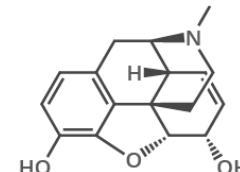
TRAMADOL

METABOLISED IN THE BODY TO A MORE POTENT OPIOID



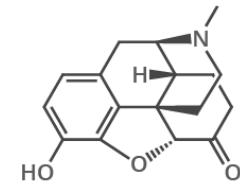
MORPHINE

THE FIRST INDIVIDUAL PLANT ALKALOID EVER ISOLATED



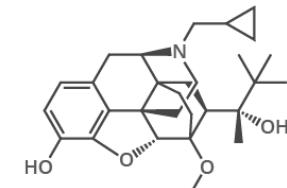
HYDROMORPHONE

MOSTLY USED INTRAVENOUSLY IN A HOSPITAL SETTING



BUPRENORPHINE

ALSO COMMONLY USED TO TREAT OPIOID DEPENDENCE



- 82% of chronic pain patients reported that their pain was “treated poorly” (National Pain Foundation, 2014).
- Over 50% of chronic pain patients complain that they have no control over managing their pain (National Pain Foundation, 2014).
- Females suffer disproportionately than males from chronic pain disorders— in some cases over 3x more (Mogil, 2012).

Current treatment options (e.g., opioids)
leave millions of people untreated.

Side effects of opioid analgesics limit their use

Miosis (pin point pupil)

Out of it (sedation)

Respiratory depression

Physical dependence

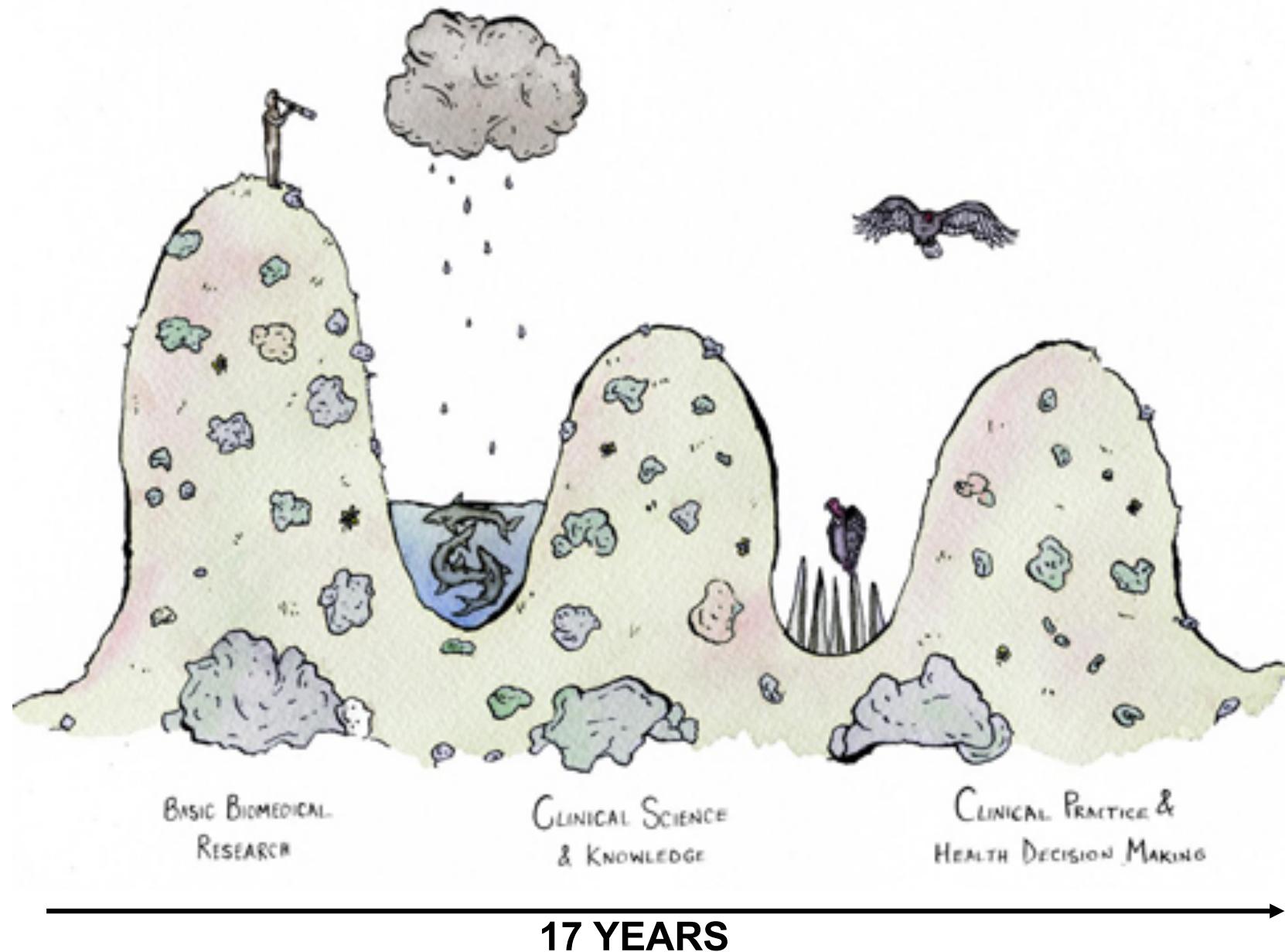
Histamine release (excessive itch)

Increased intracranial pressure

Nausea

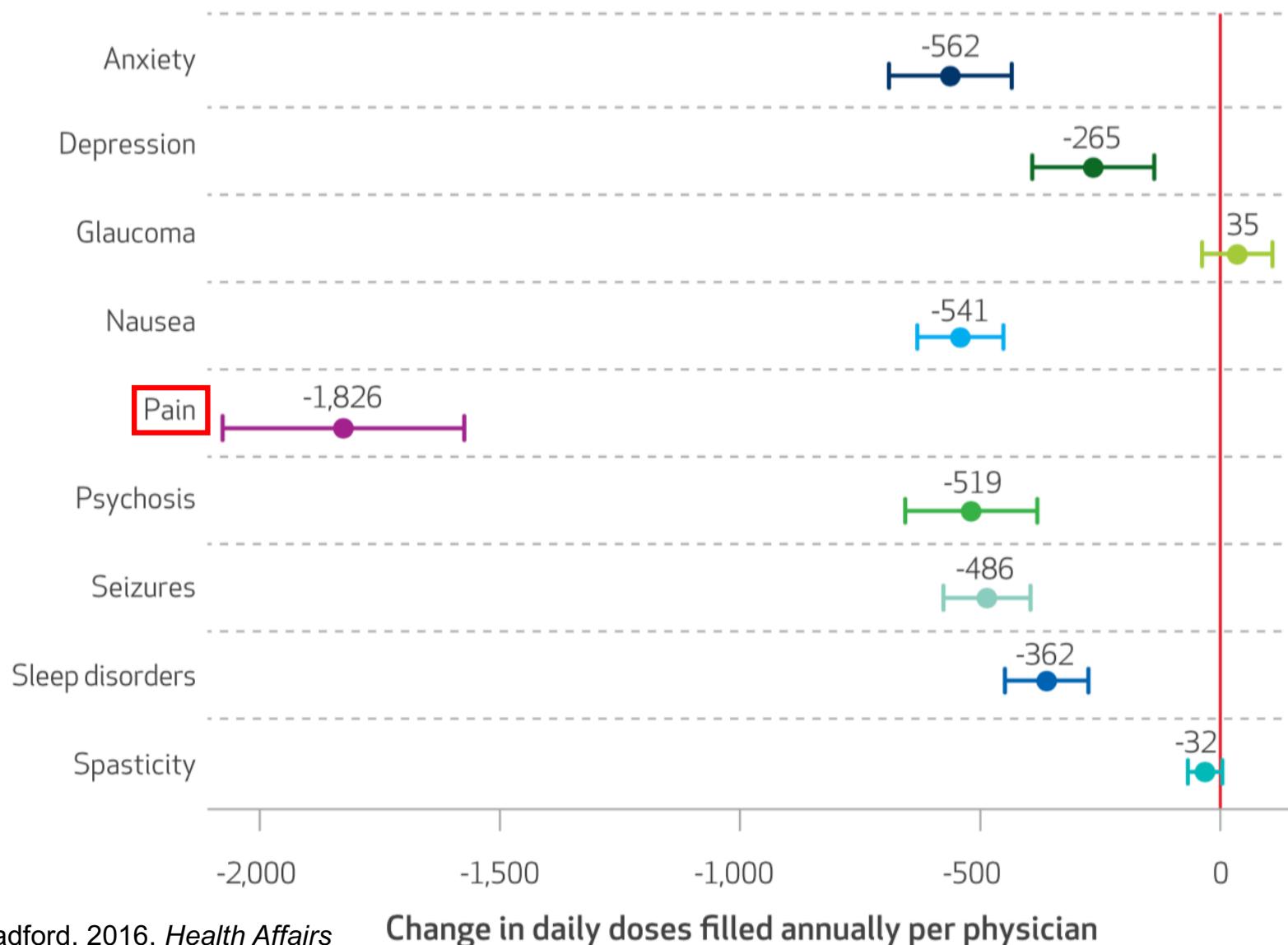
Euphoria

Bench-to-bedside translation of analgesics is SLOW

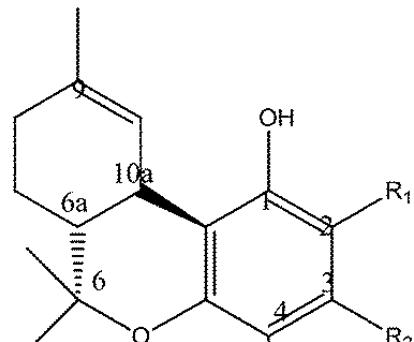


Medical marijuana laws reduce opioid prescriptions

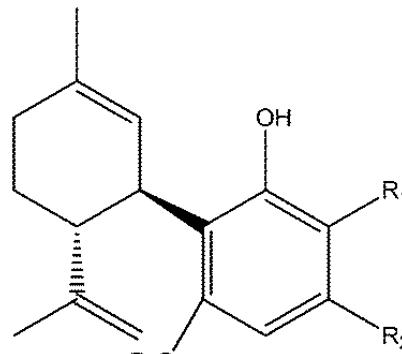
Average numbers of daily doses filled for prescription drugs annually per physician in states with a medical marijuana law, by condition categories studied, compared to the average numbers in states without a law



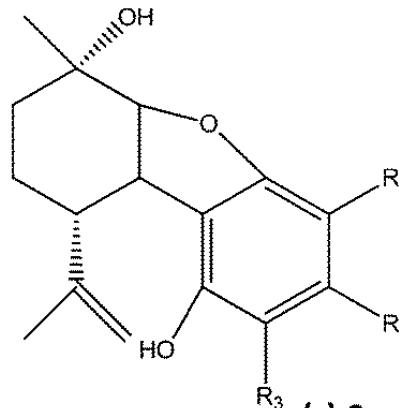
Cannabis contains 100+ cannabinoids (537 constituents total)



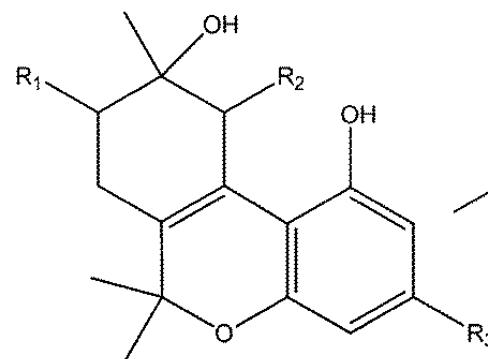
(a) Δ^9 -Tetrahydrocannabinol



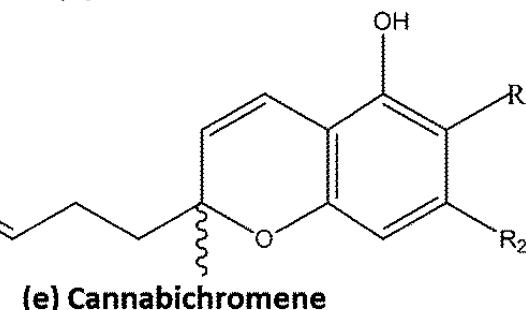
(b) Cannabidiol



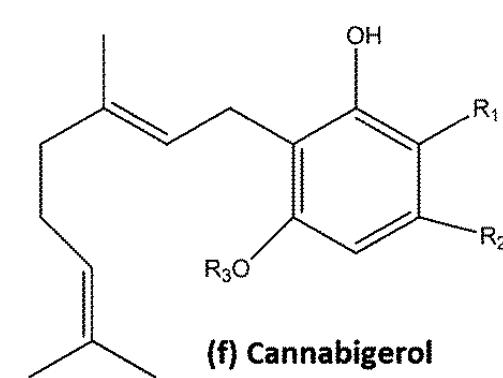
(c) Cannabielsoin



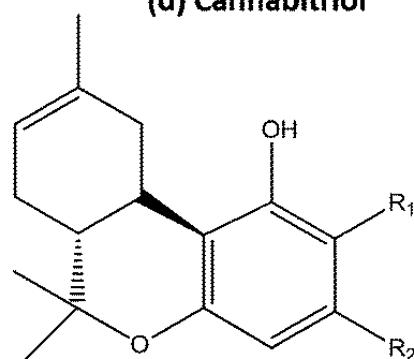
(d) Cannabitriol



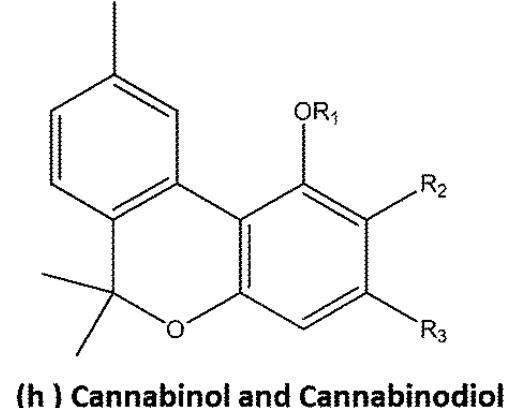
(e) Cannabichromene



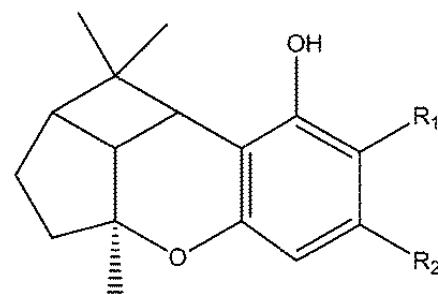
(f) Cannabigerol



(g) Δ^8 -Tetrahydrocannabinol



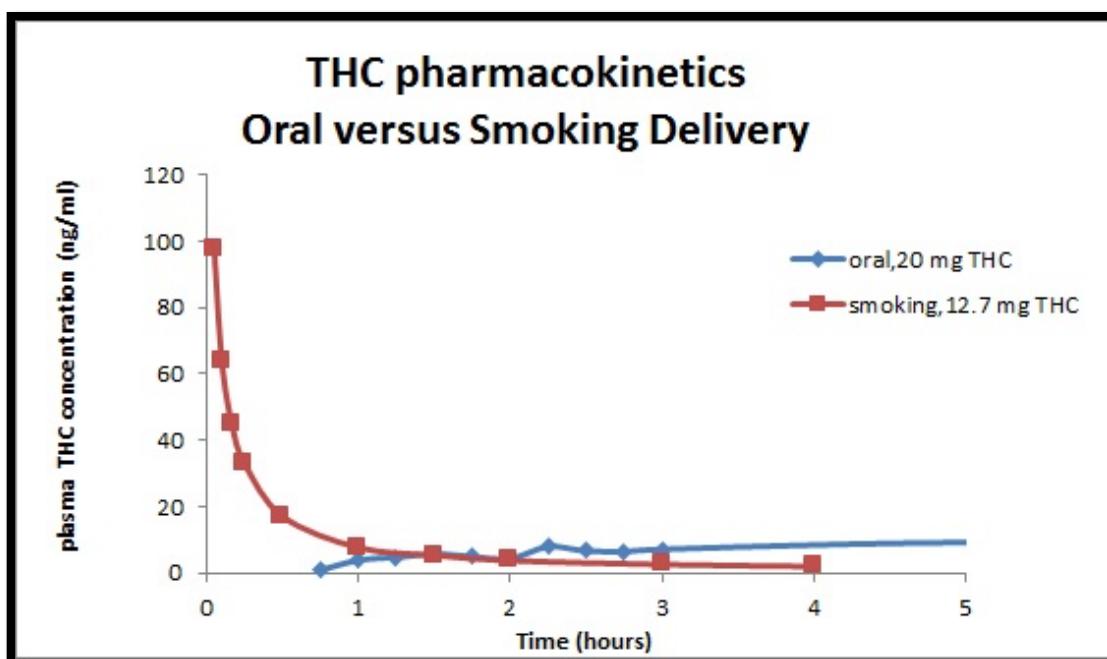
(h) Cannabinol and Cannabinodiol



(i) Cannabicyclol

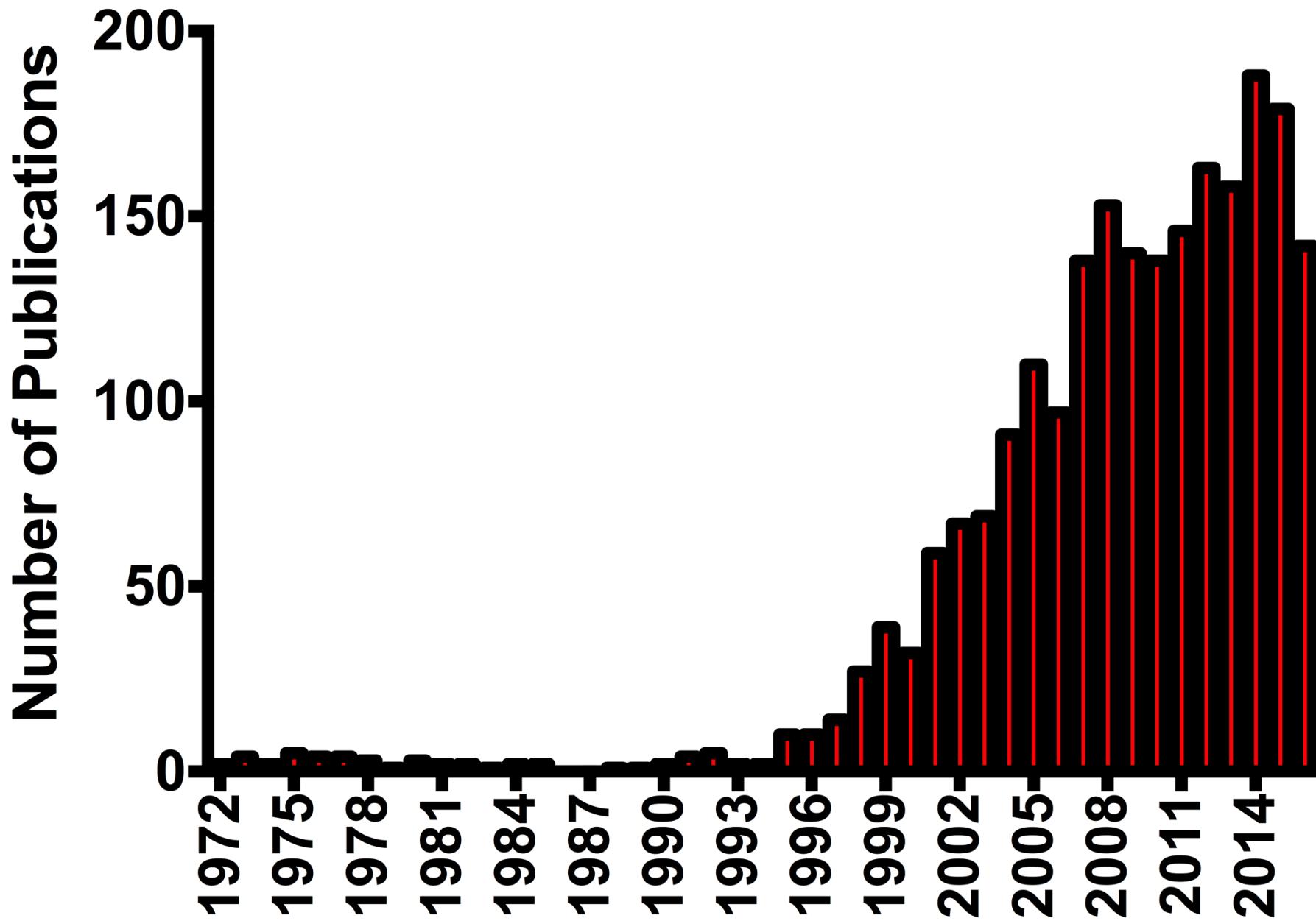
Clinical pharmacology of *Cannabis* is complex

- Elimination is slow: days to weeks; 20-35% found in urine; 80% found in feces; stored in adipose
 - Fast absorption if vaporized, slower if ingested or topical
- ✓ No constipation or respiratory suppression
- ✓ No LD₅₀

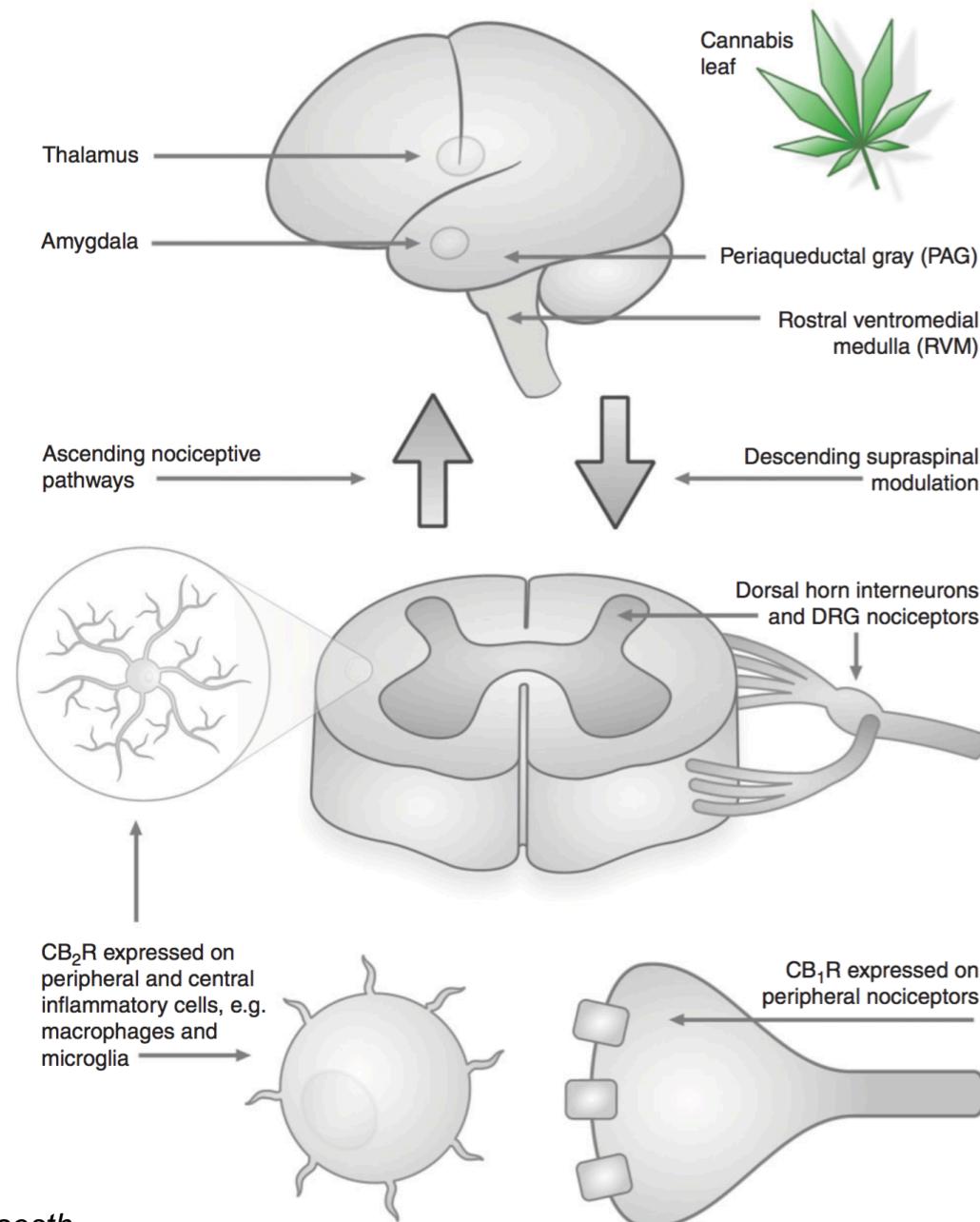


Lindgren et al., 1981,
Psychopharmacology

Cannabinoid/pain research is very new



How do cannabinoids provide pain relief?



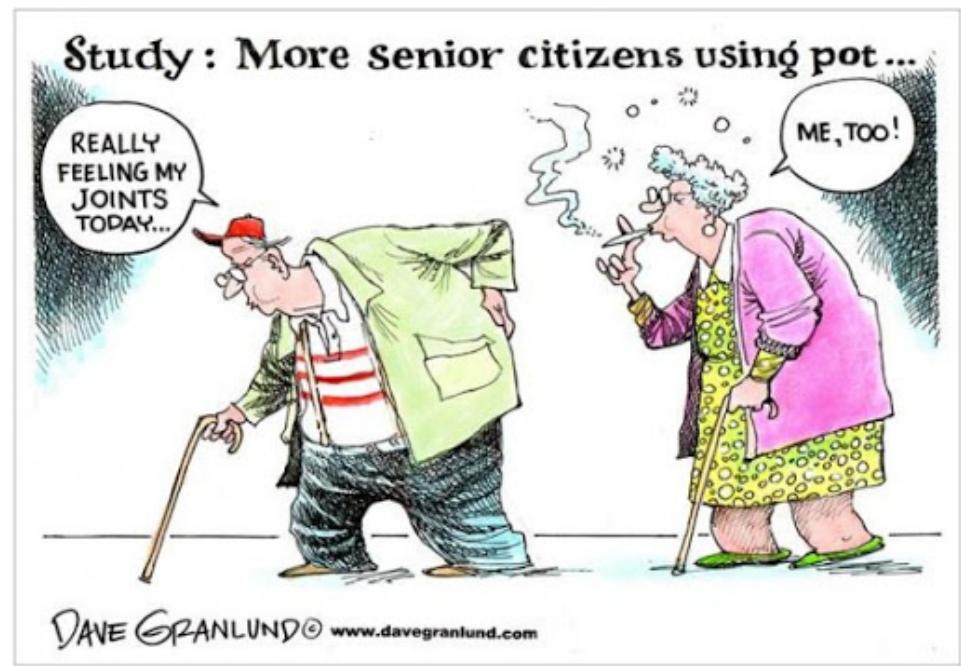
Cannabinoid-based therapies are currently on the market

- Dronabinol (Marinol): Δ^9 -tetrahydrocannabinol (Schedule III)
- Nabilone (Cesamet): Synthetic Δ^9 -tetrahydrocannabinol (Schedule II)
- Nabiximols (Sativex): Δ^9 -tetrahydrocannabinol/cannabidiol (Schedule IV)
- Medical marijuana: Δ^9 -tetrahydrocannabinol/cannabidiol/others (Schedule I)



Cannabinoids provide relief against multiple types of pain

- Myofascial pain syndrome
- Diabetic neuropathy
- **Neuropathic pain** syndrome
- Central pain syndrome
- Phantom pain
- Spinal cord injury
- **Fibromyalgia**
- Osteoarthritis
- Rheumatoid arthritis
- Discogenic back pain
- HIV-associated neuropathy
- Malignant pain
- Cancer pain
- **Headaches/ Migraine**
- Muscle cramps



Characteristics of migraine

Before an attack

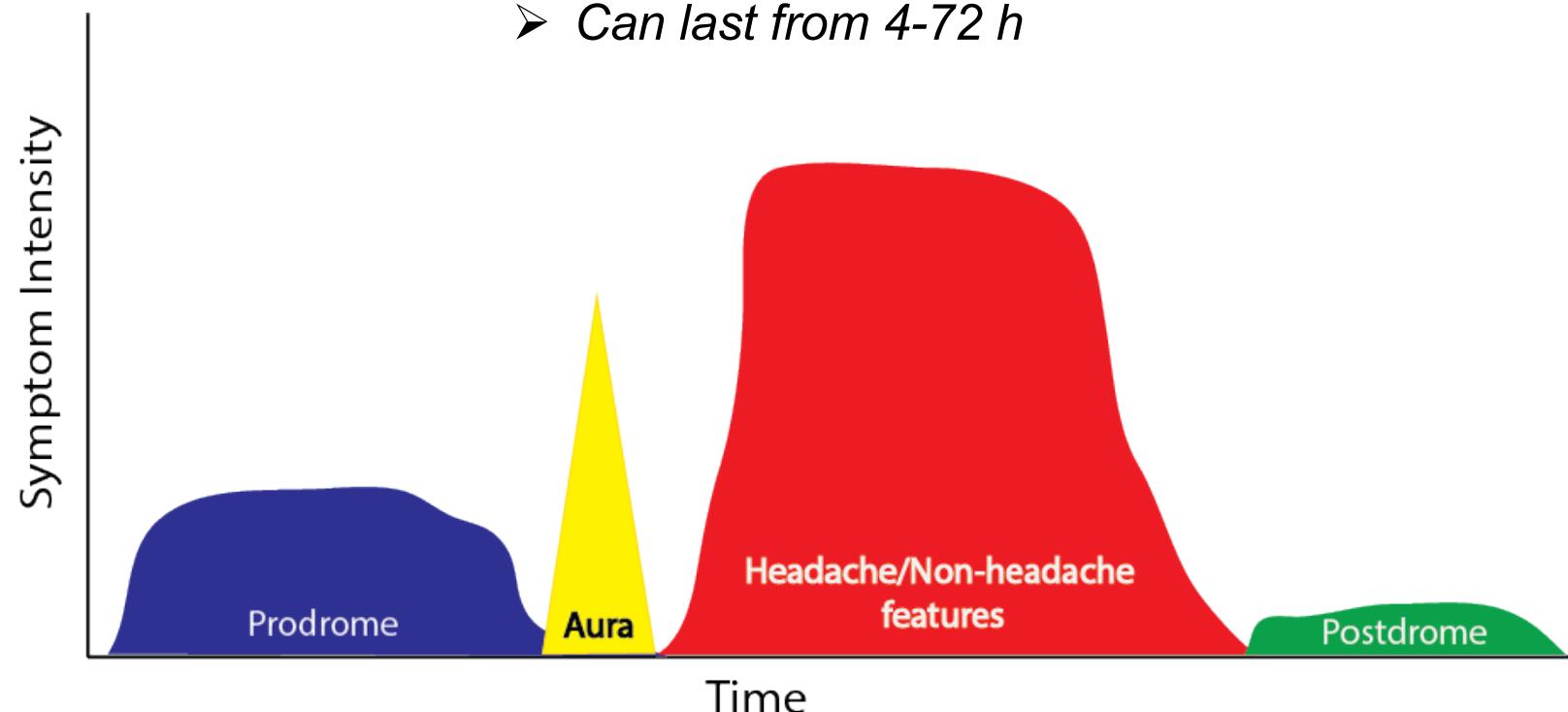
- Yawning
- Fatigue
- Food cravings
- Drowsiness or depression
- Irritability or tension
- *Occurs 24-48 h before attack*

During an attack

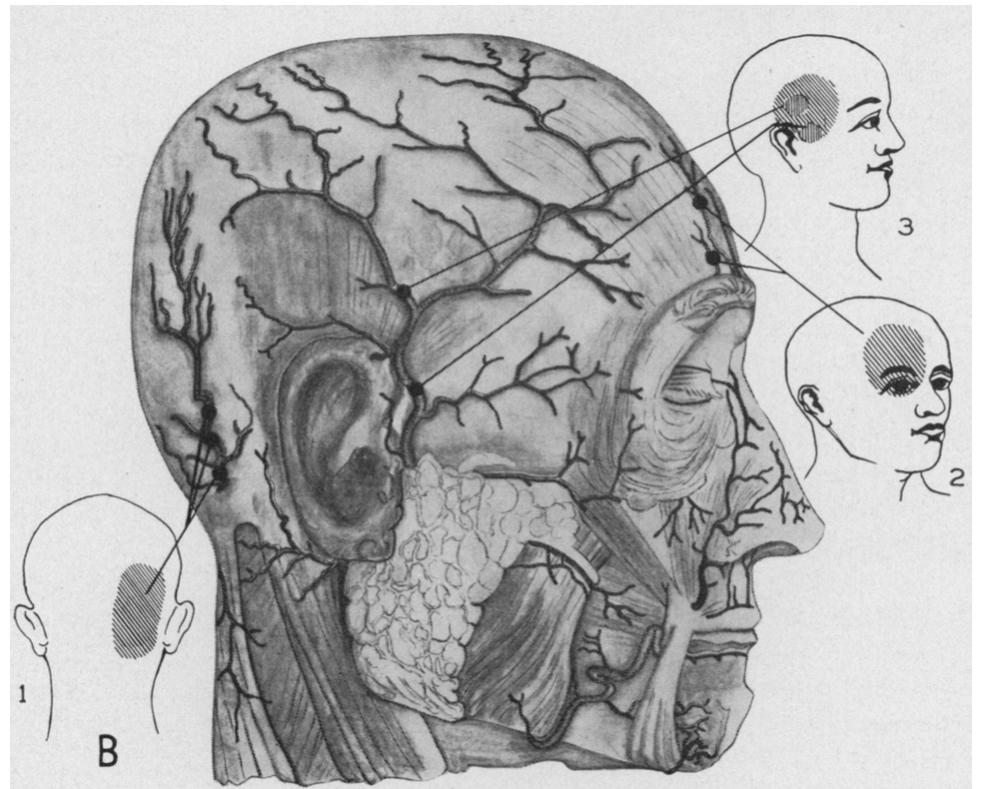
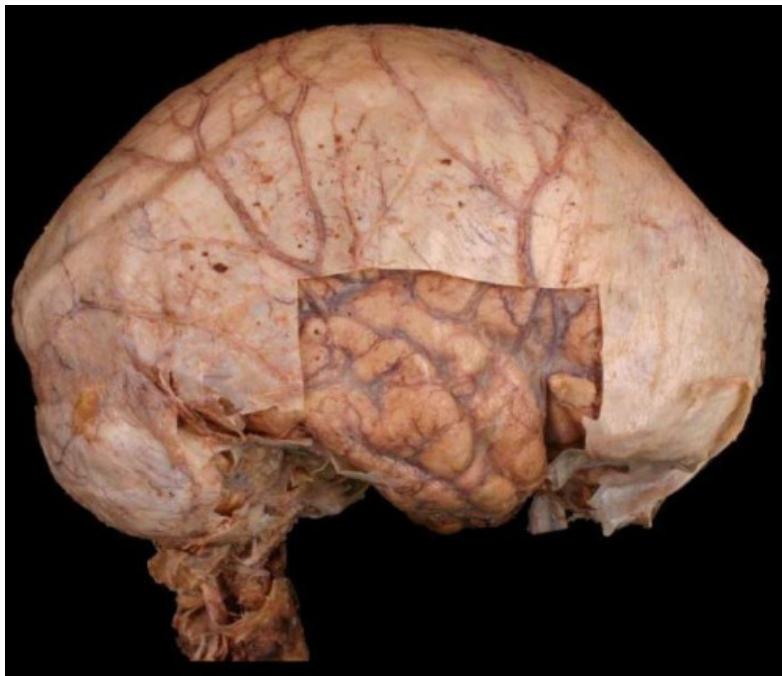
- Nausea, vomiting
- Sweating or cold hands
- Sensitivity to light and sound
- Scalp tenderness or extracephalic allodynia
- Throbbing, unilateral pain
- *Can last from 4-72 h*

After an attack

- “Hungover”
- Weakness
- Tiredness
- Mood changes
- *Can last for hours to days after attack is over*



Where do headaches come from?



Ray and Wolff, 1940, *Archives of Surgery*

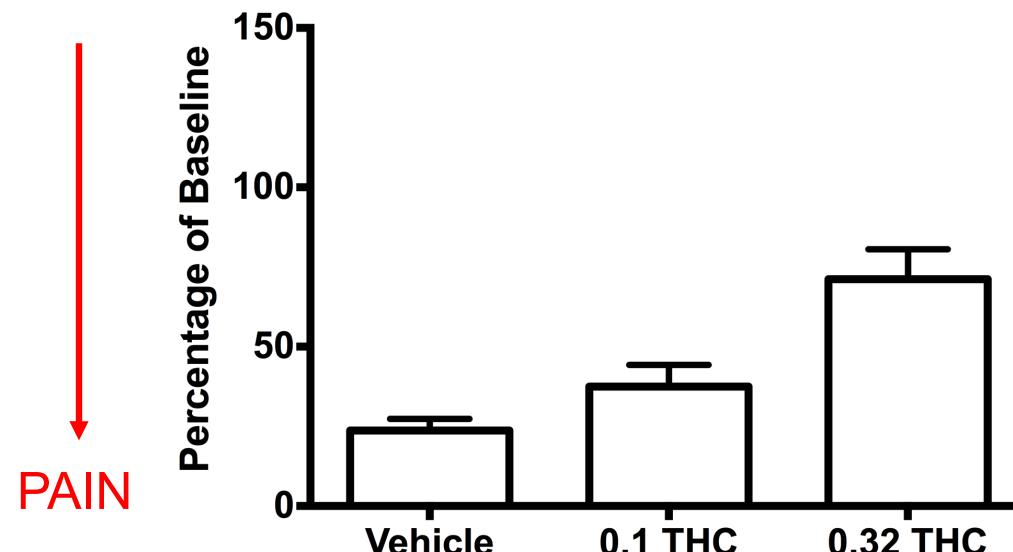
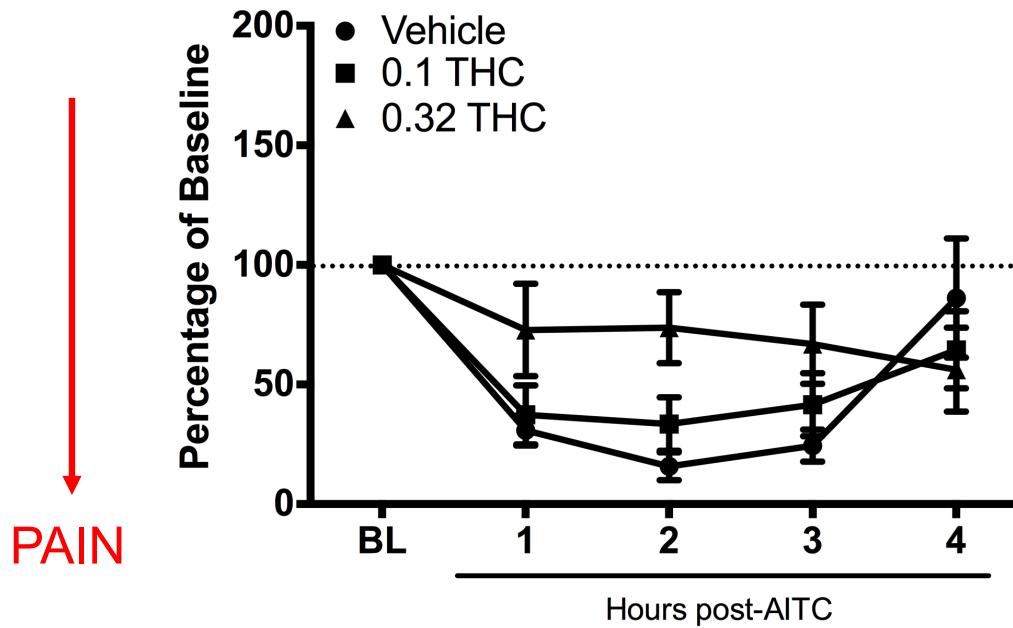
Migraine art



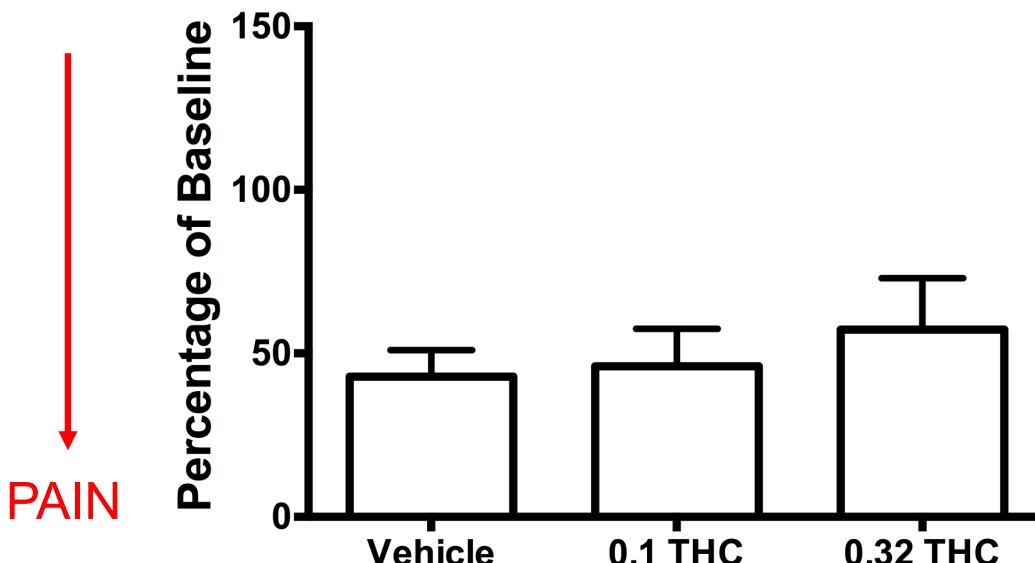
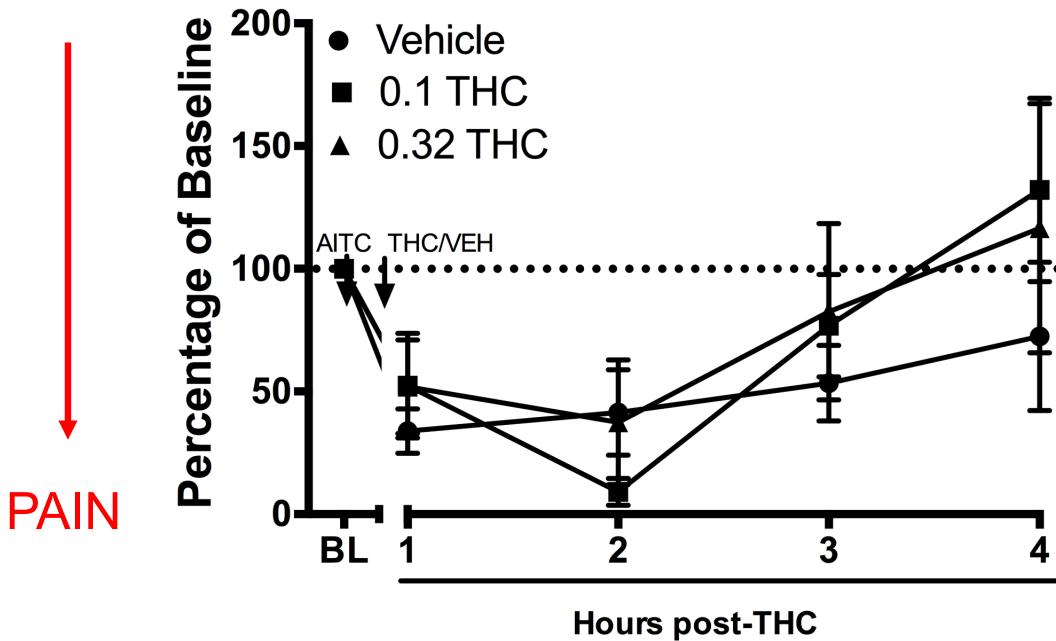
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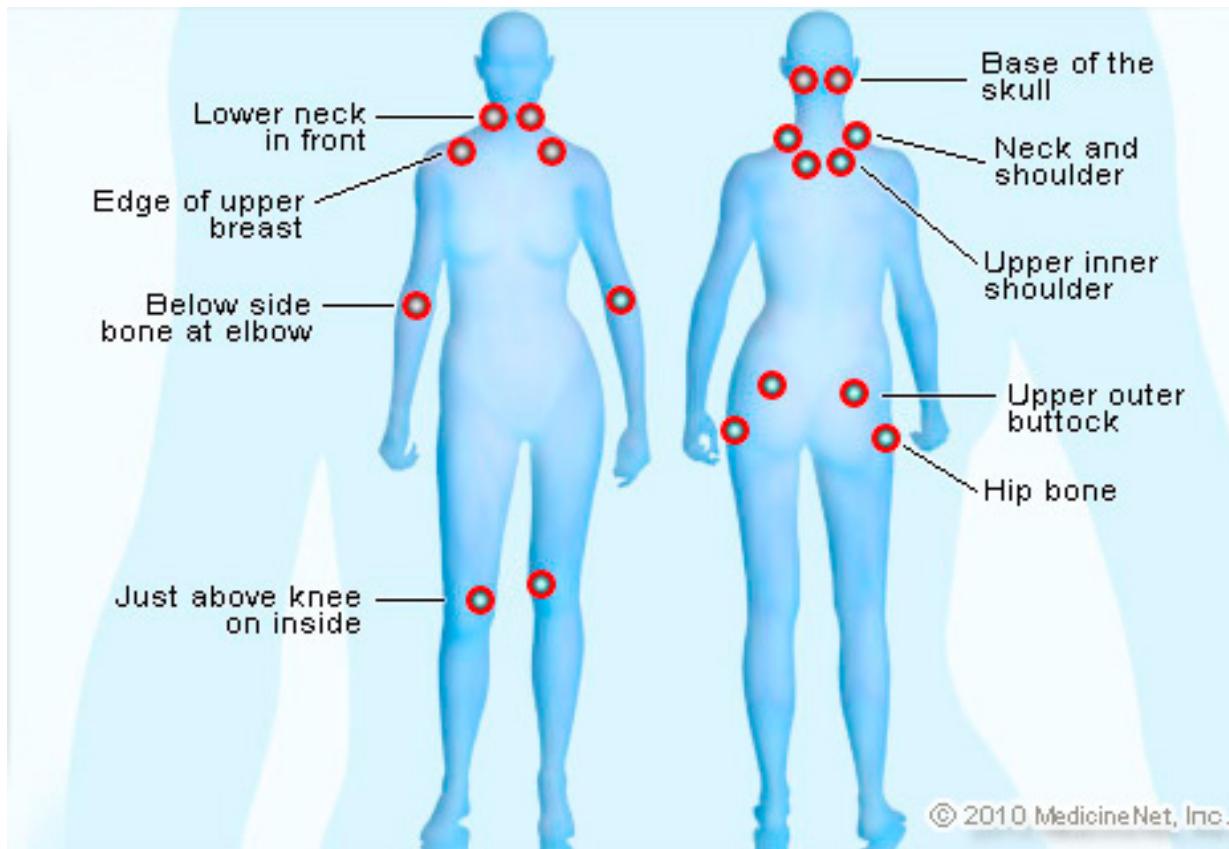
Δ^9 -THC analgesia against migraine is not perfect



Δ^9 -THC analgesia against migraine is not perfect

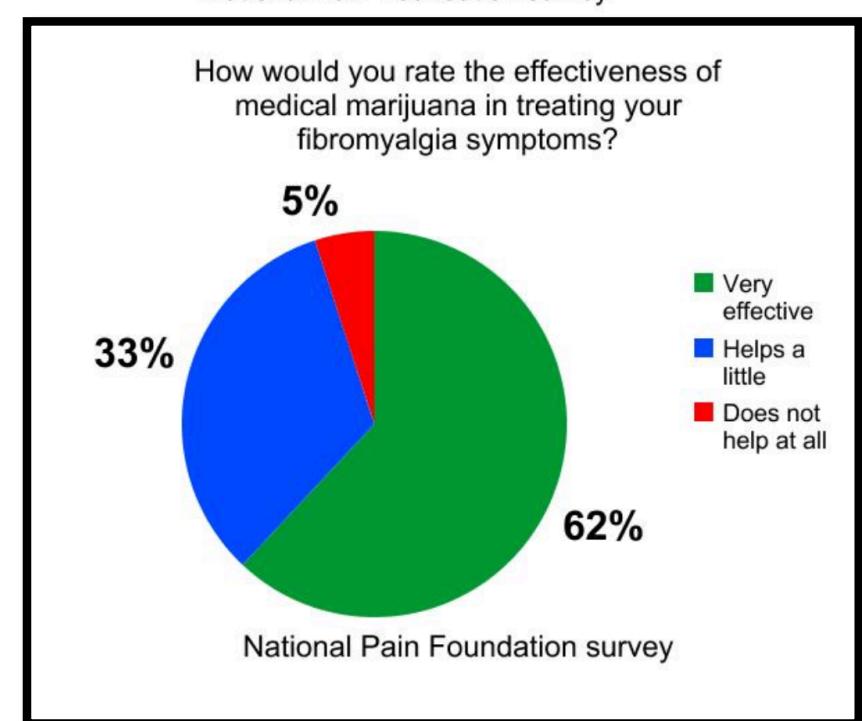
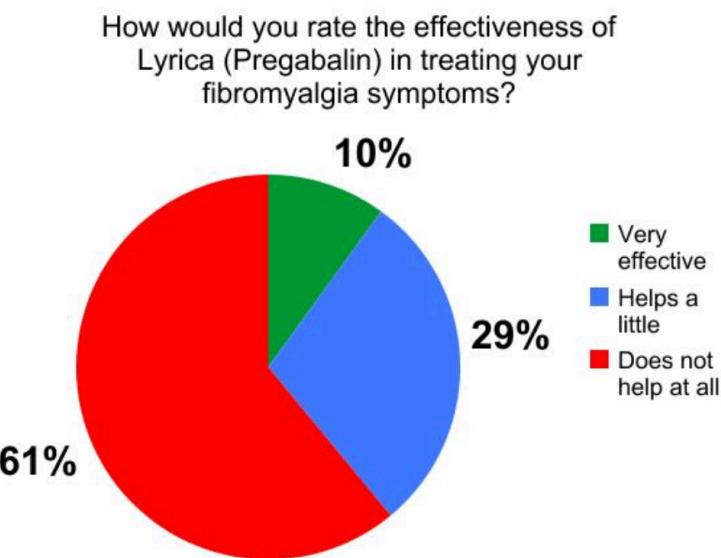
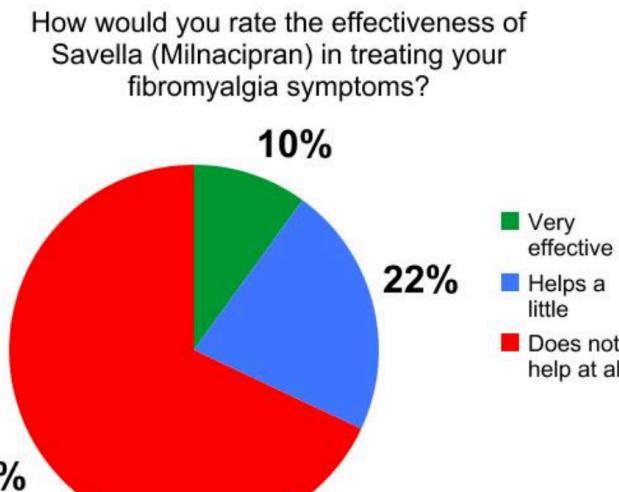
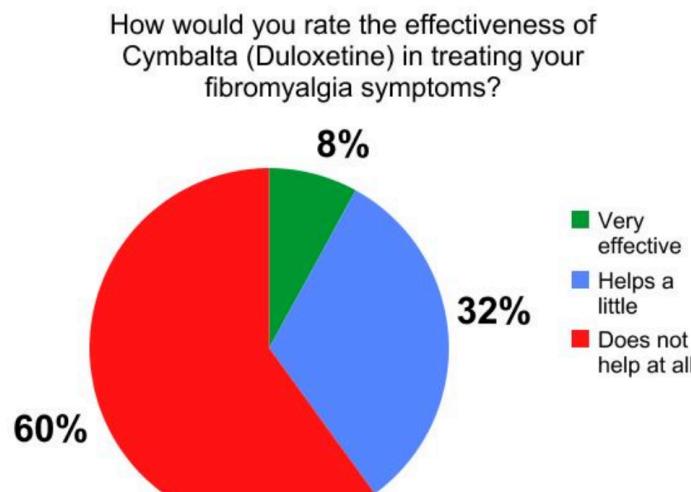


What is fibromyalgia?



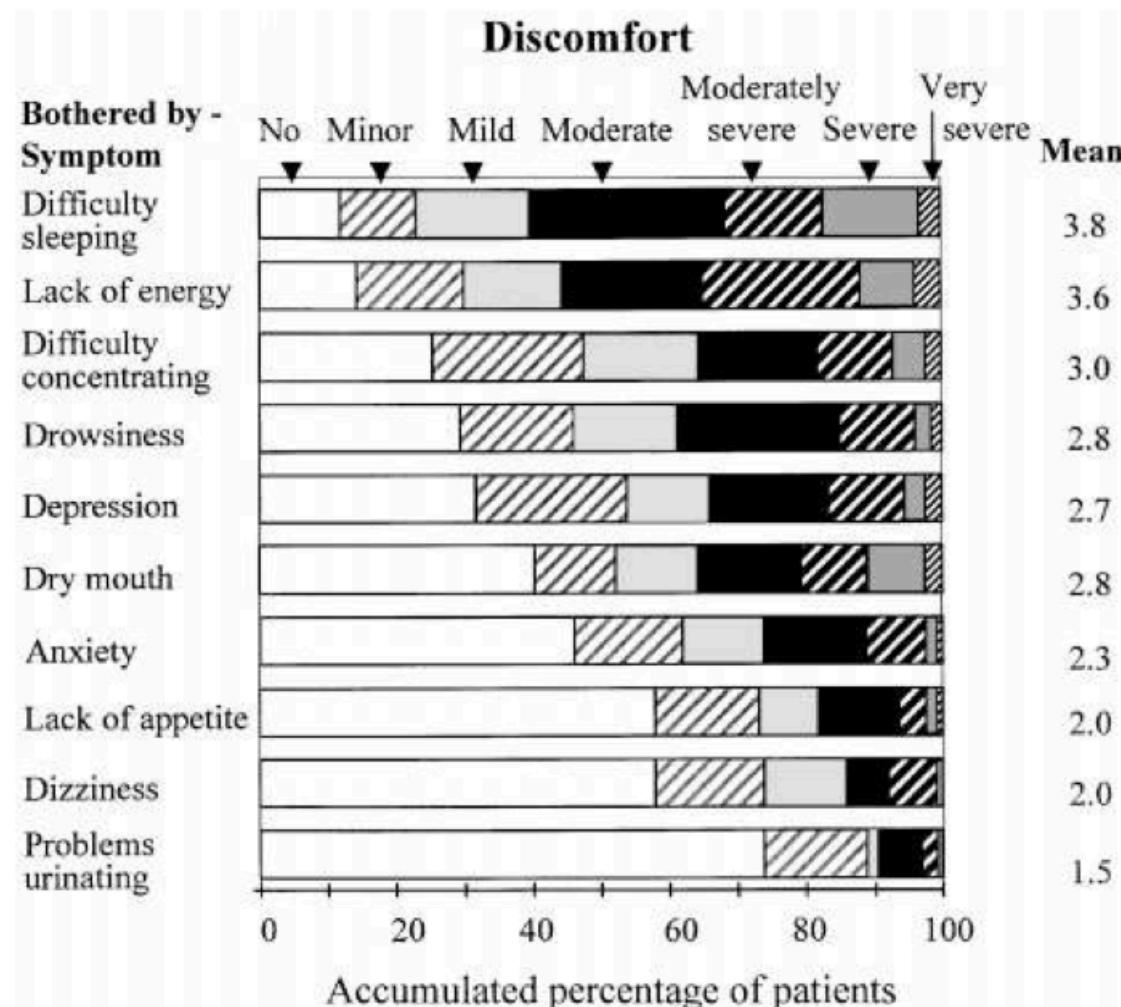
“Fibromyalgia makes your skin hurt just by the touch of your clothes. It makes your skin burn with pain.”

Cannabis is more effective against fibromyalgia pain



What is neuropathic pain?

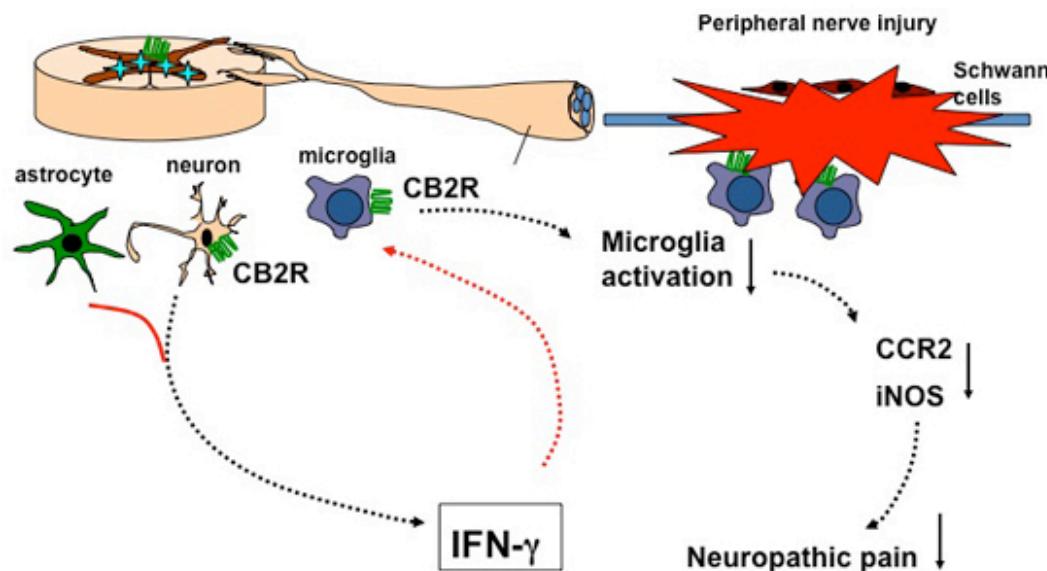
- Caused by a problem with one or more nerves such that the nerve sends pain messages to the brain in the absence of any stimulus.



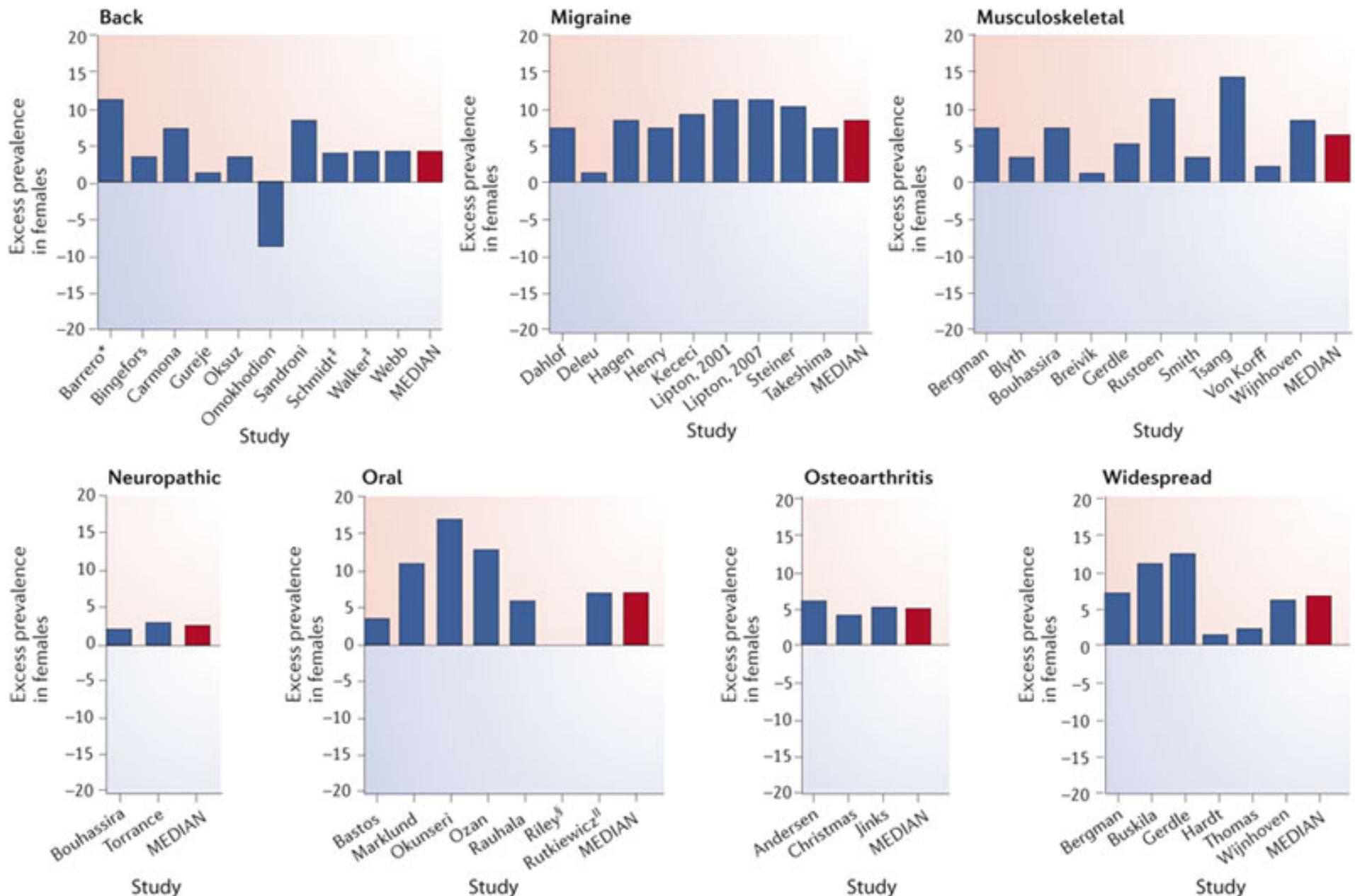
Cannabinoids may be effective for neuropathic pain

- Opioid analgesics are ineffective due to depletion of opioid receptors in the spinal cord following nerve injury.
- However, there is an upregulation of CB₁ receptors in the thalamus which may increase analgesic efficacy.

Immune responses to peripheral nerve injury



Females suffer disproportionately from chronic pain



Females are more sensitive to Δ^9 -THC analgesia



PAIN® 154 (2013) 1709–1717

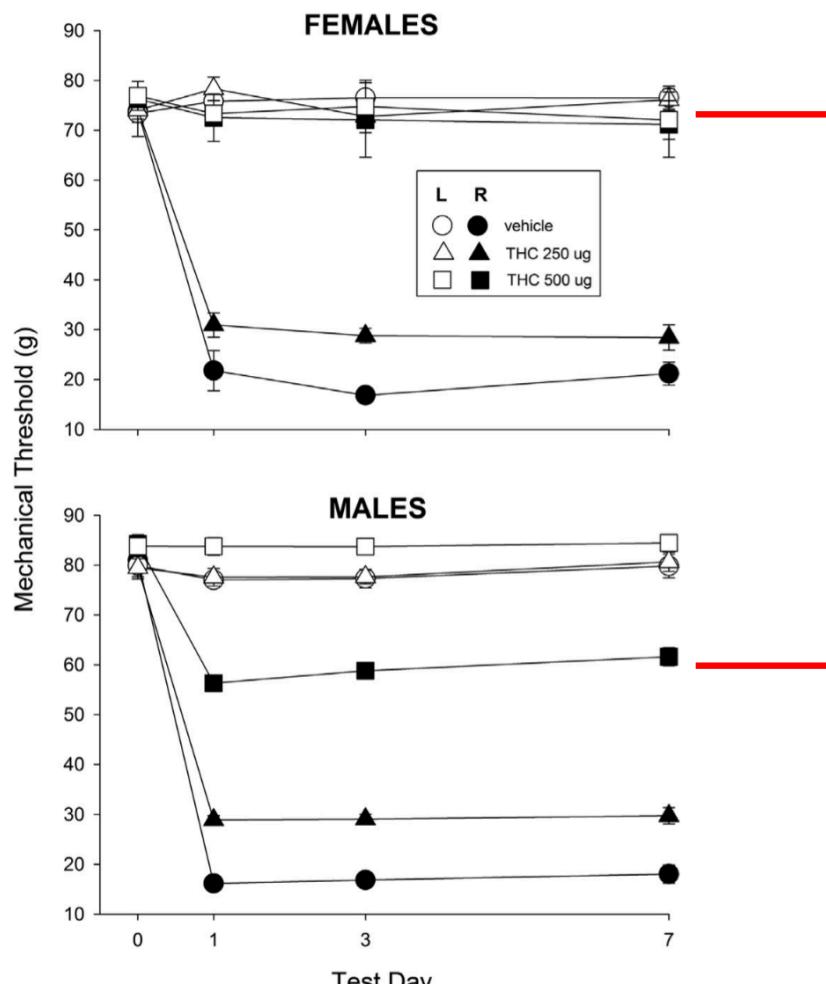
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www.elsevier.com/locate/pain

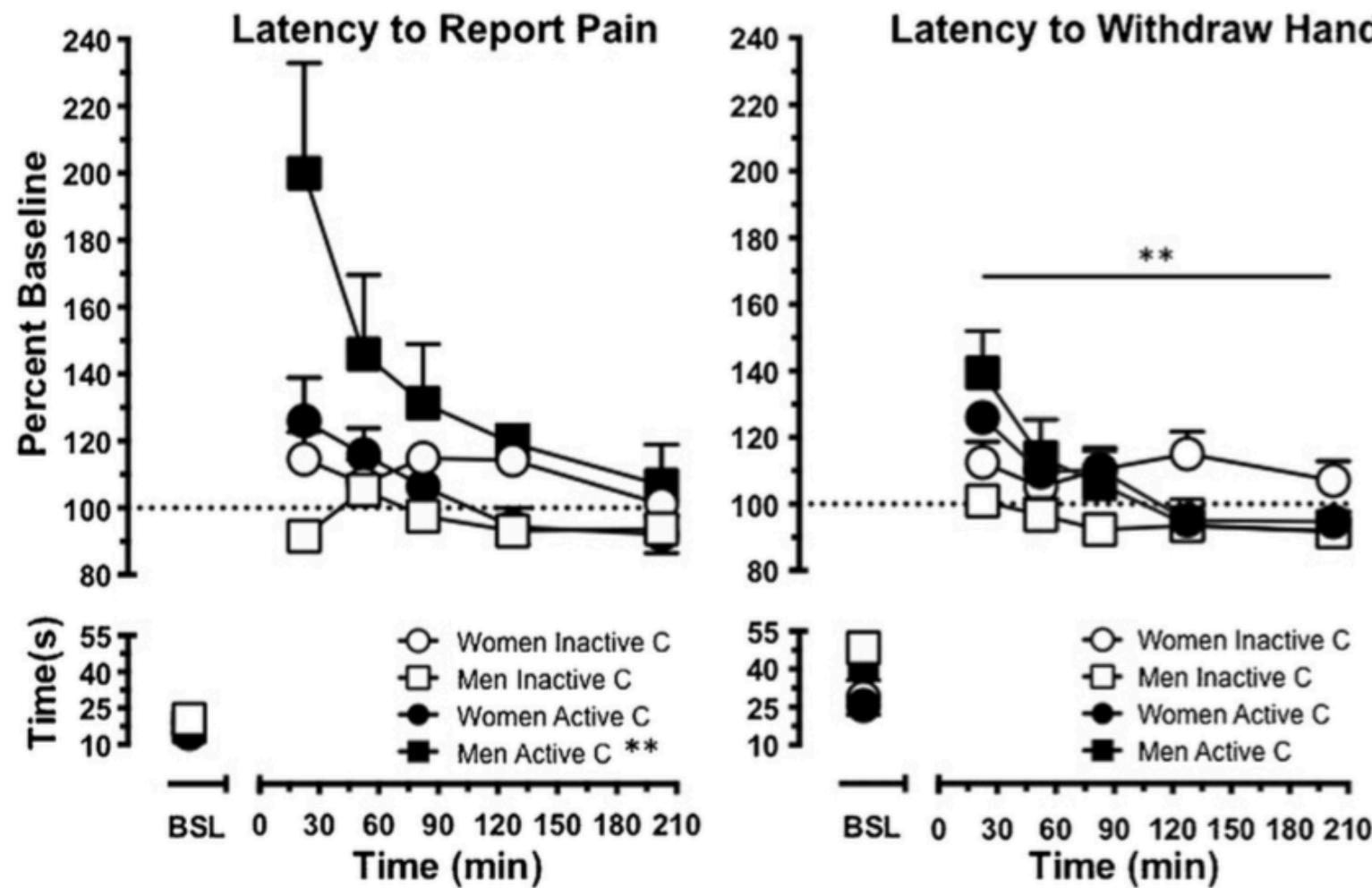
Sex differences in anti-allodynic, anti-hyperalgesic and anti-edema effects of Δ^9 -tetrahydrocannabinol in the rat

Rebecca M. Craft *, Ram Kandasamy, Seth M. Davis

Department of Psychology, Washington State University, Pullman, WA 99164-4820, USA



Males are more sensitive to *Cannabis* analgesia



Advantages of cannabinoids over traditional analgesics

- Minimal side effects (no constipation or respiratory depression)
- At least 1 year of use is not associated with long-term negative consequences in adults
- No LD₅₀
- *Cannabis* use for pain is not associated with increased vascular, metabolic, blood, renal, musculoskeletal, gastrointestinal, pulmonary, or immune system disorders

Unanswered questions surrounding CB analgesia

- Limit psychoactivity?
- Peripherally-restricted CB agents?
- Cannabinoid x opioid synergy?
- Legal status?
- Is **marijuana** a ‘magic bullet’ for chronic pain patients?

Questions?
