12-3-2021

Lessons of the Opioid Epidemic - December 3, 2021

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Cautionary Tales of Cannabis and Opioids for Chronic Pain

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Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against a sea of troubles
And by opposing end them?

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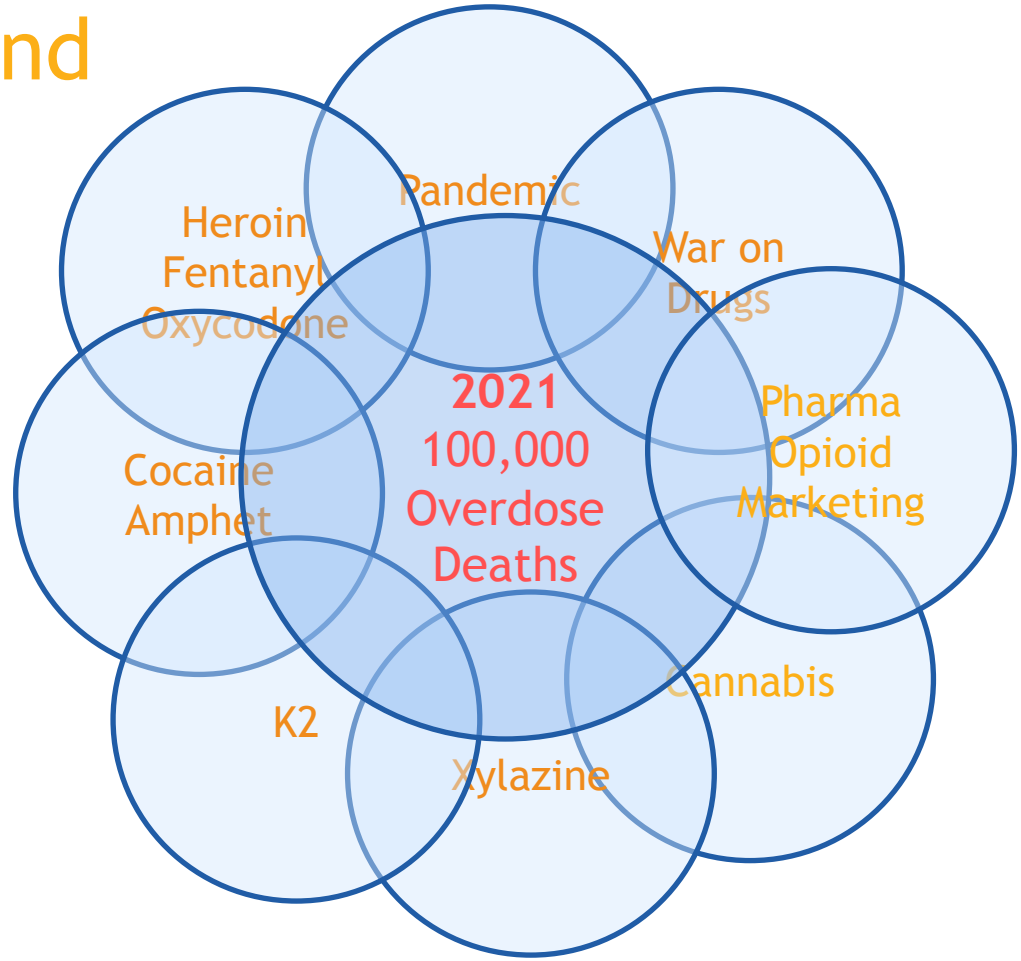
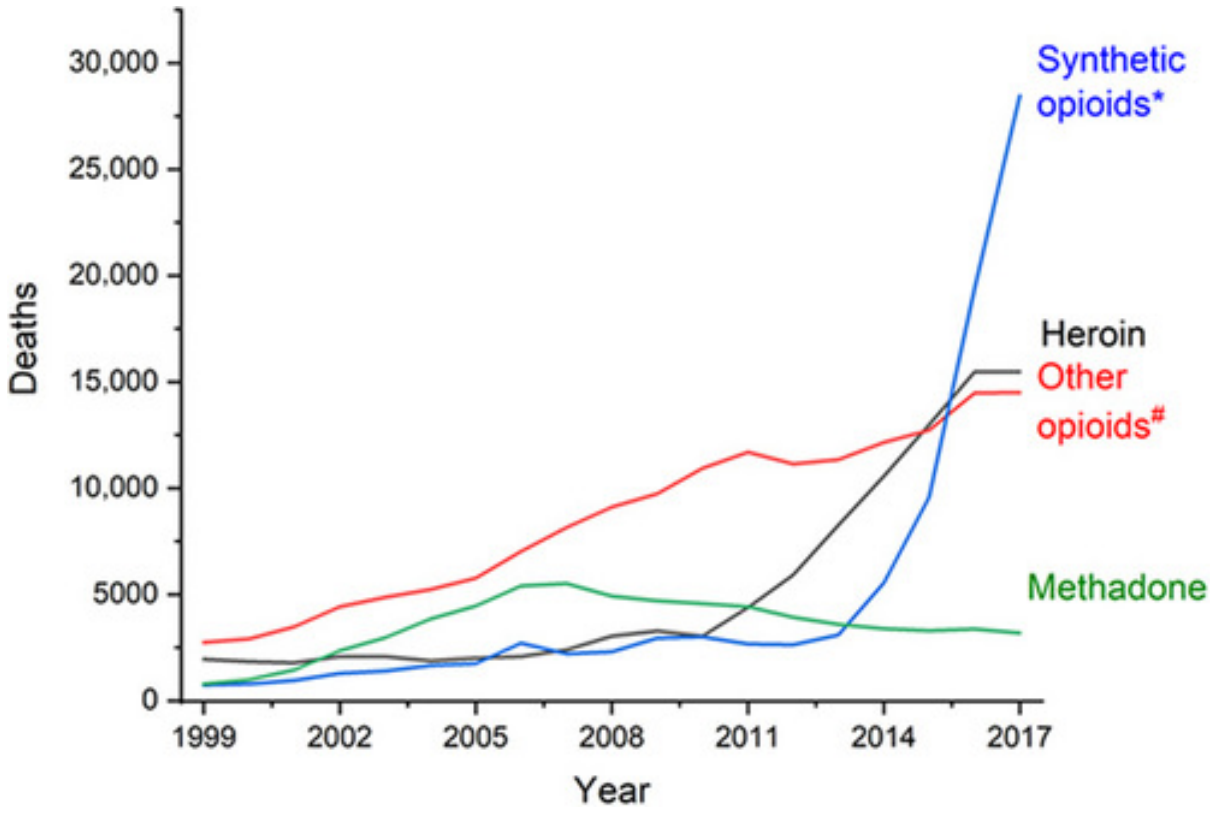
Background



2018: Prescribed and recreational opioids implicated in 70% of OD deaths
32% of OD deaths directly attributable to prescription opioids.[1]

[1]National Institute on Drug Abuse. Overdose Death Rates. Available at: https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates. Accessed July 13, 2020.

Opioid Abuse and Synthetic Opioids

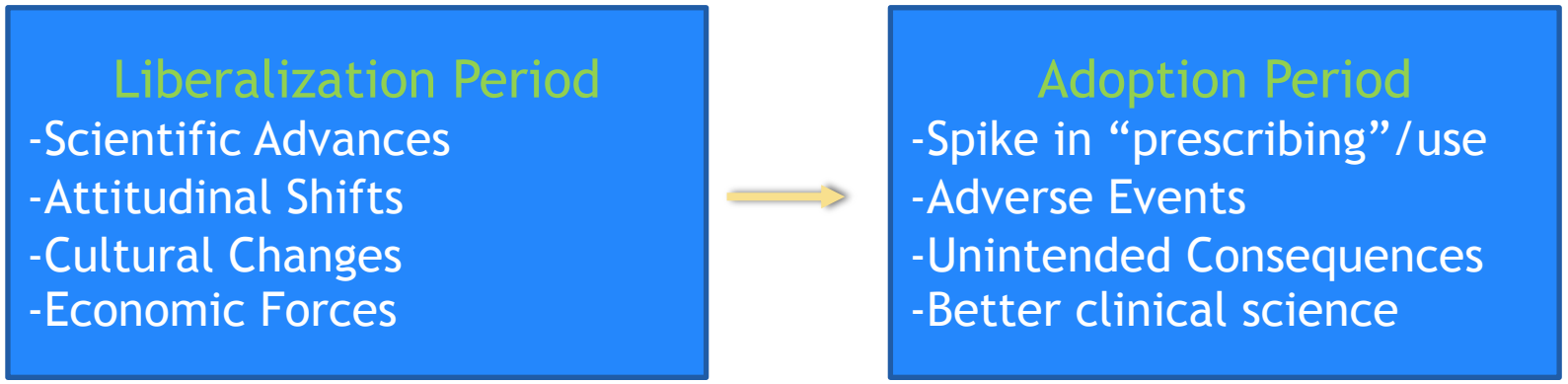


Kreek et al., Sci. Adv. (2019) **Current status of opioid addiction treatment and related preclinical research, Volume: 5, Issue: 10, 11 pp.**

What past missteps can be avoided?

- What viewpoints, cultural changes, economic forces and events set the stage mainstreaming both drugs for pain?
- Did scientific data support using these agents for pain?
- Can we identify a sequence of building momentum then increasing adoption of each drug for pain?

Time frame construct



1989-1999 Opioid Liberalization
Purdue Pharma and the Oxycontin Story

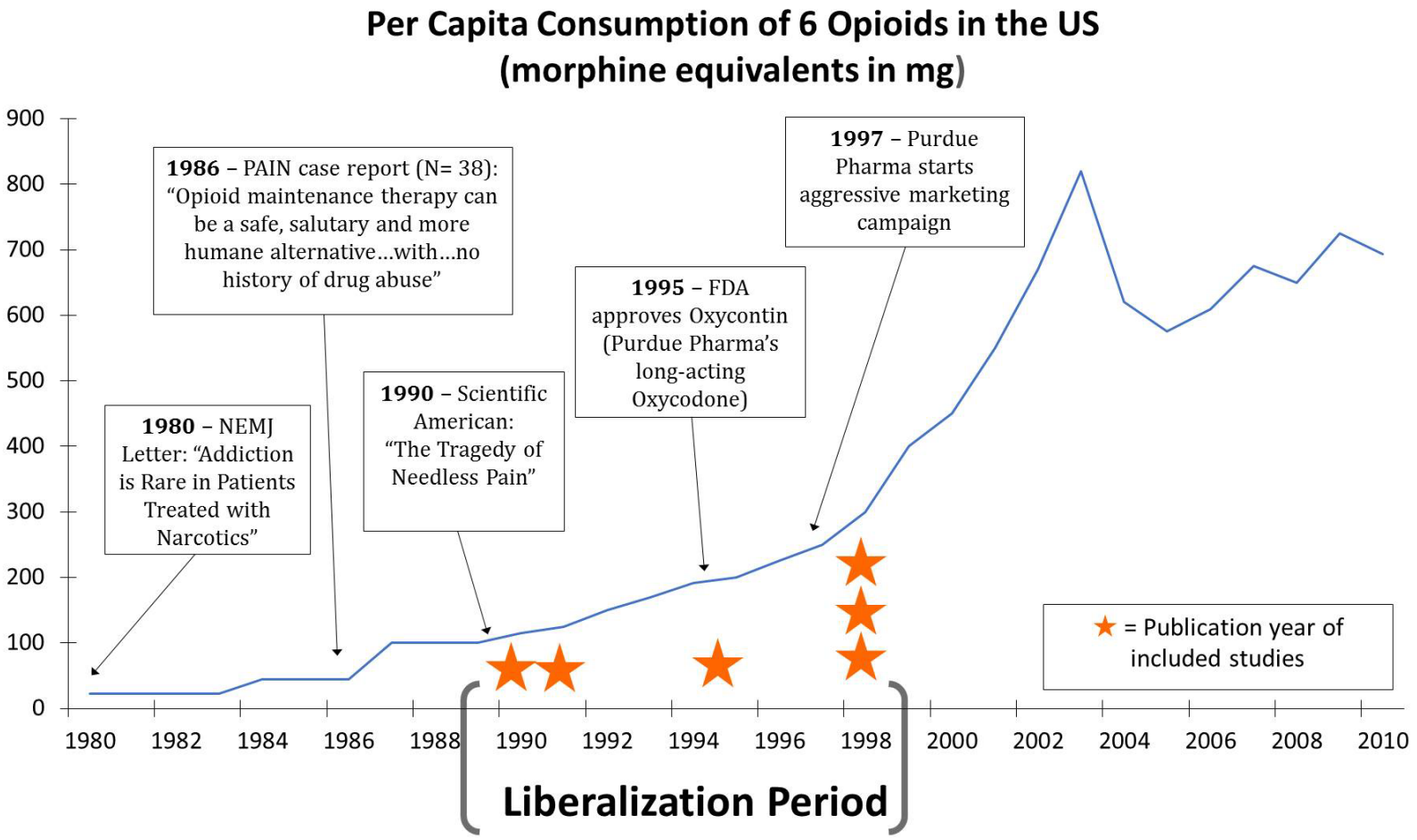
- 1980's: Prominent studies supporting opioid use for CNCP[2]
- 1995-1996: FDA approval and launch of Oxycontin
- 1996-1999: Major spike in opioid prescriptions begins[3]
- 1995-2001: Purdue doubles size of sales force over 6-year period
  Early 2000s: Aggressive marketing campaigns for opioids
- Retail opioid market grows 32-fold in 2 decades:
  from < $250M sales in 1992 to $8B in 2015

[2]Guy GP, Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. MMWR Morb Mortal Wkly Rep 2017;66(26):697–704.

[3]deShazo RD, Johnson M, Eriator I, Rodenmeyer K. Backstories on the US opioid epidemic. good intentions gone bad, an industry gone rogue, and watch dogs gone to sleep. Am J Med 2018;131(6):595–601.

Opioids: 10-year liberalization period

1989 - 1999



1998-2008 Medical Cannabis Liberalization
Story of State Governments vs. Federal Agencies

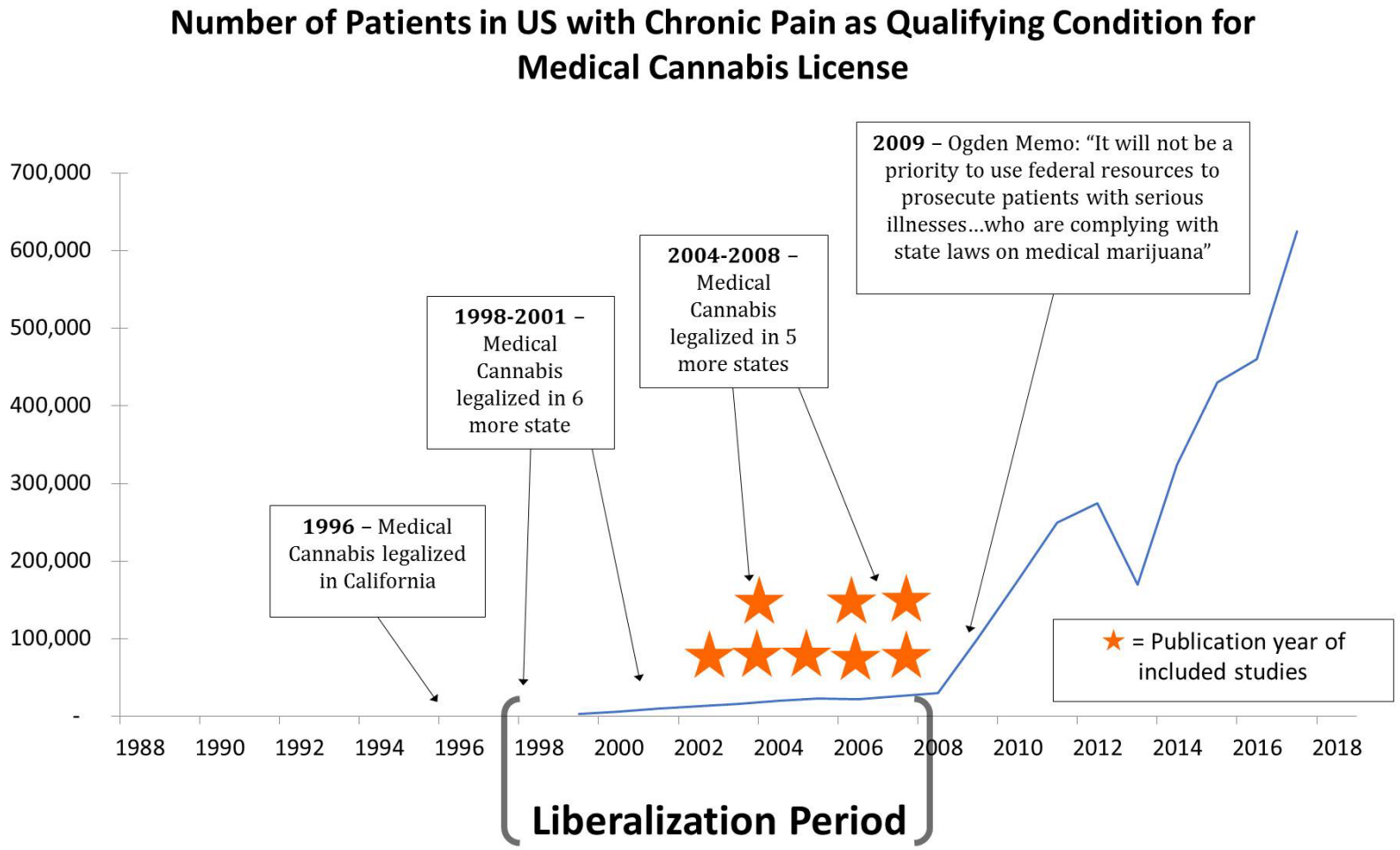
- 1980's and 1990's: Political and legal turmoil over DEA scheduling
- 1996: California is first state to legalize medical cannabis
- 1997: NEJM editorial on rescheduling and regulating medical cannabis[4]
- 1997: NIH states insufficient evidence for therapeutic use[5]
- 1998-2001: Medical cannabis legalized in 7 more states
- 2004-2008: 5 more states legalize medical cannabis
- 2008: Use for chronic pain spikes after gradual increase
- 2009: Memo from Deputy AG David Ogden

[4]Kassirer JP. Federal foolishness and marijuana. N Engl J Med 1997;336(5):366–7.

[5]Voelker R. NIH panel says more study is needed to assess marijuana's medicinal use. JAMA 1997;277(11):867–8.

Cannabis: 10-year liberalization period

1998 - 2008



Liberalization Period Studies

What did we know? and When did we know it?

- Performed narrative synthesis of opioid and cannabis studies
- Meta-analyzed pain outcomes from liberalization RCTs
- Applied Cochrane GRADE criteria for quality and confidence

Studies supporting spike in use

GRADE Evaluations of Published Studies*

	Liberalization Period	# Studies Reviewed	# Studies to Meta-Analysis	Quality of Evidence	Confidence	Major Concerns
Opioids	1989-1999	6	4	High Moderate Low Very Low	Low to No Confidence	Publication bias All pharma supported Handling of dropouts Missing outcomes Methods vague No ITT analysis Meaningful effect size, low quality
Cannabis	1998-2008	10	6	High Moderate Low Very Low	Low to No Confidence	Publication bias High % pharma supported Allocation issues Blinding problems Modified ITT Low effect size, better quality Less common pain conditions

***2 opioid trials** and **4 cannabis trials excluded** from meta-analysis because outcomes could not be pooled

All reported sponsoring companies been sued for opioid-related activities:

-**Purdue Frederick** in 2017 and **Ortho-Mcneil Pharmaceuticals** in 2018 for deceptive marketing

-**Grunenthal Group** in 2019 for a kickback scheme

Momentum behind advocacy

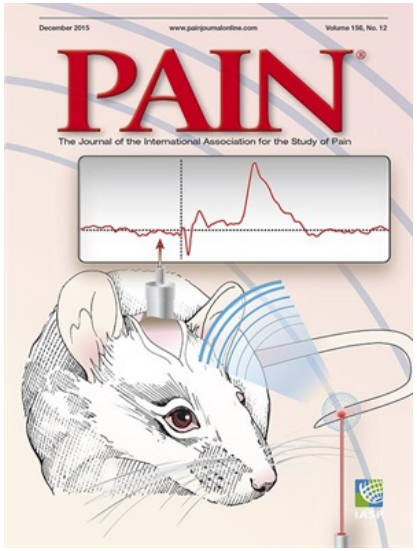
OPIOIDS

- Socio-Cultural
  - Tragedy of Needless Pain
  - Pain Awareness
  - JCAHO Accreditation standard
- Medical Opinion
  - Underutilized Analgesics
  - Provide and protect access to care
  - Artificial Cancer vs. NCP dichotomy
  - Improve QOL, eg better sleep, function
- No-Data Prevailing Narrative
  - *Industry-led*
  - Opioids rarely addictive
  - Opioids safe in hands of general clinicians for common pain problems
  - Opioids safer than NSAIDS, adjuvants
  - Opioids have almost no dose ceiling

CANNABIS

- Socio-Cultural
  - Cannabis is benign
  - Questioning war on drugs
  - Controversy over Schedule I status
- Medical Opinion
  - Cannabis minimally addictive
  - Cannabis has good safety profile
  - Cannabis may be opioid-sparing
  - Improve QOL, eg better appetite & sleep
- No-Data Prevailing Narrative
  - *Citizen-led*
  - Cannabis rarely addictive
  - Generally safe
  - Extrapolation of relative safety to medically complex contexts
  - Safer than opioids, NSAIDS, adjuvants

Best Recent Studies



Oxycodone in CLBP (2015)

PAIN

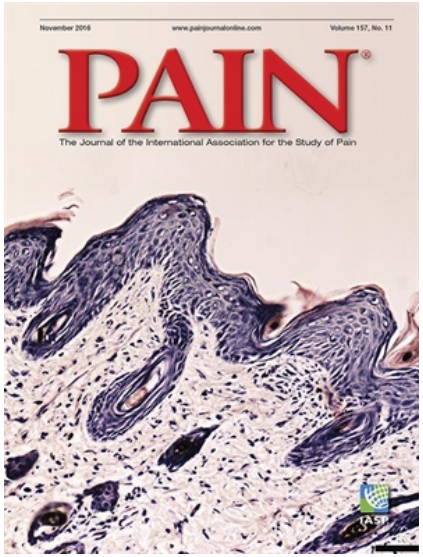
A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain

Nathaniel Katz[a,b,*], Ernest A. Kopecky[c], Melinda O'Connor[c], Robert H. Brown[d], Alison B. Fleming[c]

Abstract

Opioid analgesics are commonly used for the treatment of chronic low back pain (CLBP); however, abuse potential is a major concern. This study used a randomized, double-blind, placebo-controlled, enriched-enrollment randomized-withdrawal study design to evaluate the safety, tolerability, and analgesic efficacy of an abuse-deterrent formulation of extended-release oxycodone, Xtampza ER, in opioid-naive and opioid-experienced adults with moderate-to-severe CLBP. Patients entered an open-label titration phase (N 5 740); those who were successfully titrated on Xtampza ER ($40 to #160 mg oxycodone hydrochloride equivalent per day) were randomized to active drug (N 5 193) or placebo (N 5 196) for 12 weeks. Primary efficacy results showed a statistically significant difference in average pain intensity from randomization baseline to treatment week 12 between the Xtampza ER and placebo groups (mean [6SE], 21.56 [0.267]; *P*, 0.0001). All sensitivity analyses results supported the primary result of the study. Secondary efficacy outcomes indicated that Xtampza ER vs placebo had more patients with improvement in patient global impression of change (26.4% vs 14.3%; *P*, 0.0001), longer time-to-exit from the study (58 vs 35 days; *P* 5 0.0102), and a greater proportion of patients with $30% (49.2% vs 33.2%; *P* 5 0.0013) and $50% (38.3% vs 24.5%; *P* 5 0.0032) improvement in pain intensity. There was less rescue medication (acetaminophen) use in the Xtampza ER treatment group than in the placebo group. Xtampza ER had an adverse event profile consistent with other opioids and was well tolerated; no new safety concerns were identified. In conclusion, Xtampza ER resulted in clinically and statistically significant efficacy in patients with CLBP.

Keywords: Opioid, Oxycodone, Low back pain, Abuse deterrent, Randomized controlled trial



Buprenorphine in CLBP (2016)

PAIN

Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study

Joseph Gimbel[a,*], Egilius L.H. Spierings[b], Nathaniel Katz[c,d], Qinfang Xiang[e], Evan Tzanis[f], Andrew Finn[g]

Abstract

A buccal film of buprenorphine (BBUP) was evaluated for safety and efficacy in a multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study in opioid-experienced patients (30 to #160 mg/d morphine sulfate equivalent) with moderate to severe chronic low back pain taking around-the-clock opioid analgesics. Patients' opioid doses were tapered to #30 mg morphine sulfate equivalent before open-label titration with BBUP (range, 150-900 mg every 12 hours). Patients who responded (received adequate analgesia that was generally well tolerated for 14 days) were randomized to receive buprenorphine (n 5 254) or placebo (n 5 257) buccal film. The primary efficacy variable was the change from baseline to week 12 of double-blind treatment in mean average daily pain-intensity scores using a rating scale of 0 (no pain) to 10 (worst pain imaginable). In the intent-to- treat population, mean pain scores were 6.7 after opioid taper and declined to 2.8 after the BBUP titration period. After randomization, mean pain scores were lower in the BBUP group than in the placebo group; the difference between groups in the mean change from baseline to week 12 was 20.98 (95% CI, 21.32 to 20.64; *P*, 0.001). A significantly larger percentage of patients receiving BBUP than placebo had pain reductions $30% and $50% (*P*, 0.001 for both). In the double-blind portion of the study, the only adverse event reported more frequently with BBUP than placebo and in $5% of patients was vomiting (5.5% vs 2.3%). These findings demonstrate the efficacy and tolerability of BBUP in opioid-experienced patients taking around-the-clock opioid treatment for chronic low back pain.

Keywords: Chronic low back pain, Buccal buprenorphine, Opioid-experienced patients

Opioids for CLBP

- Chronic pain affects @ 1/3 of American adults
- CLBP is 5th most common reasons for office visits
- $635 billion annually in medical costs and lost productivity
- At least 30% of low back pain patients treated with opioids

Xtampza ER in patients with moderate-to-sever chronic low back pain. Katz Nl, Kopecky EA, O'Connor M, Brown RH, Fleming AB. PAIN156(12):2458-2467, 2015.

Buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain. Gimbel J, Spierings ELH, Katz N, Xiang Q,Tzanis E, Finn A. PAIN157(11):2517-2526, 2016.

Opioids for CLBP

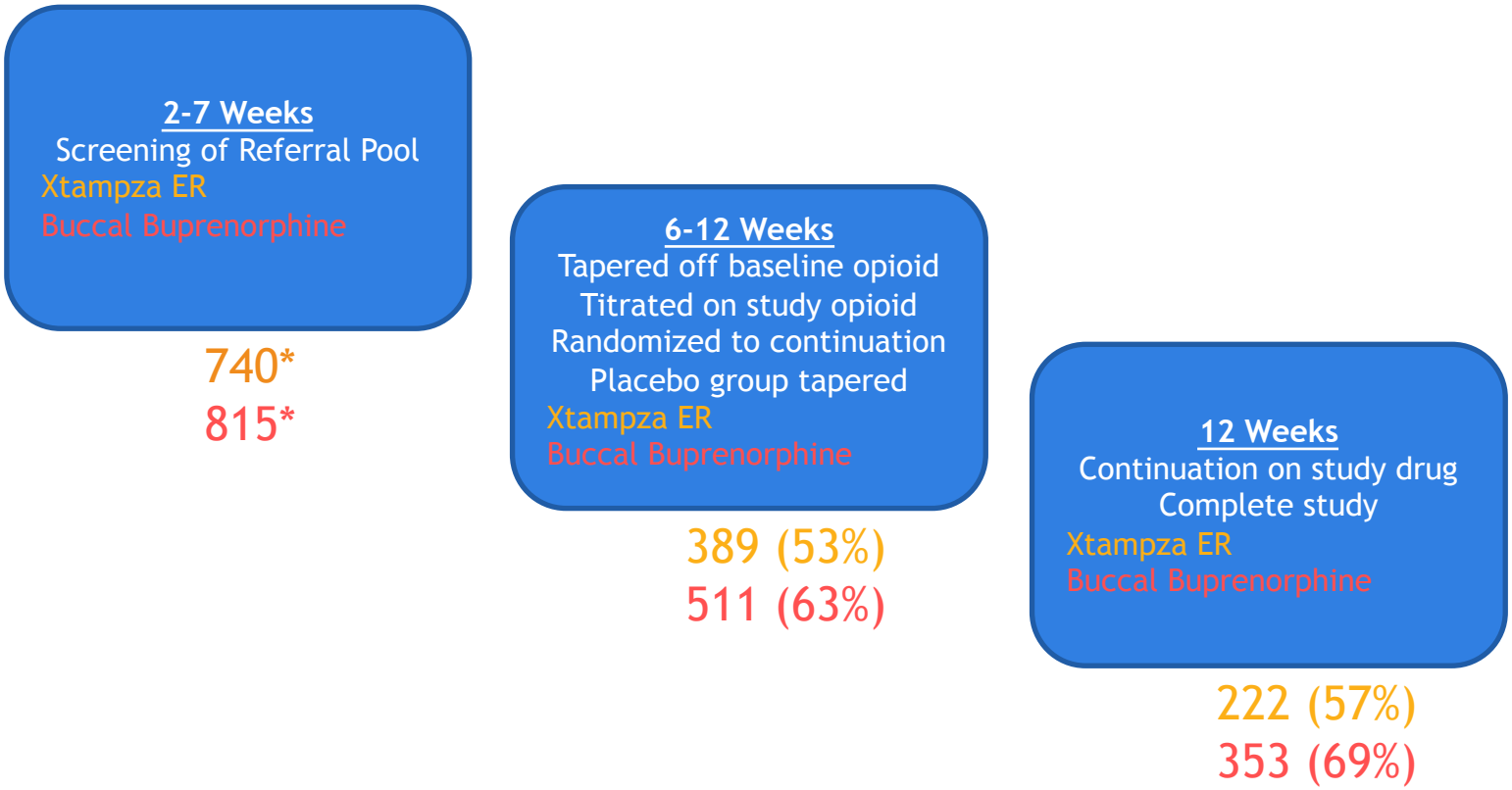
Xtampza ER in patients with moderate-to-sever chronic low back pain. Katz Nl, Kopecky EA, O'Connor M, Brown RH, Fleming AB. PAIN156(12):2458-2467, 2015.

Buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain. Gimbel J, Spierings ELH, Katz N, Xiang Q,Tzanis E, Finn A. PAIN157(11):2517-2526, 2016.

- 400-500 screened CLBP subjects w good response to drug
- 40+ centers across US
- No SUD, no opioid failures, no symptomatic depression
- Non-neuropathic CLBP, minimal other pain C/Os
- Pain scores $\geq$ 5/10
- Followed on study drugs for 12 weeks
- Stable doses of adjuvants, APAP, NSAIDS permitted
- Stable, effective antidepressant doses permitted
- 98-99% compliance
- Pharma supported

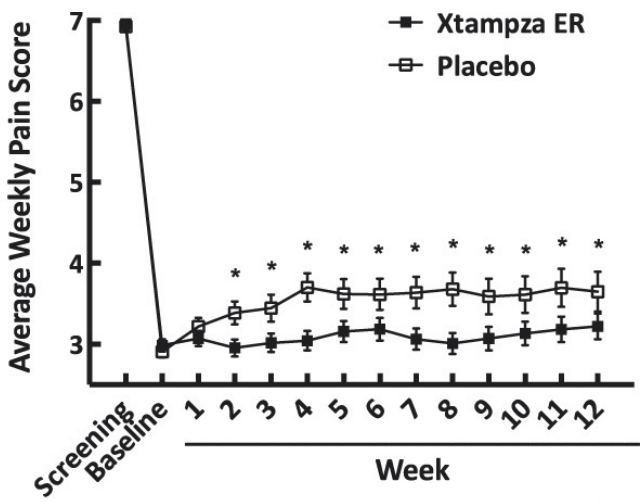
Opioids for CLBP

Katz et al. (2015), Gimbel et al. (2016)



*49-62% of original screened subjects

Enriched Design Opioid Continuation
Moderate to Severe CLBP

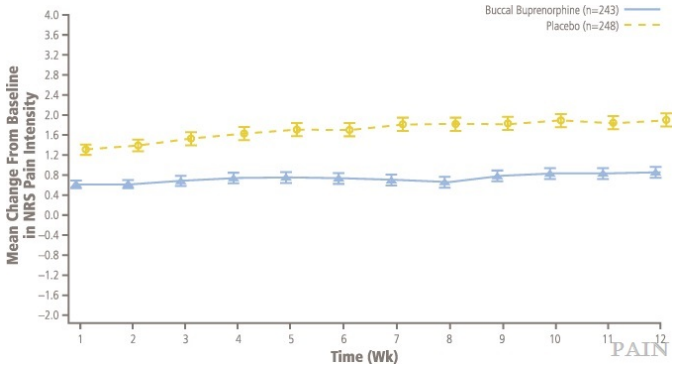


ER = extended-release

Katz Nl, Kopecky EA, O'Connor M, Brown RH, Fleming AB. PAIN156(12):2458-2467, December 2015.

Average weekly pain score (intent-to-treat population; mean [±SE])

(n=389, 53% of screened group)



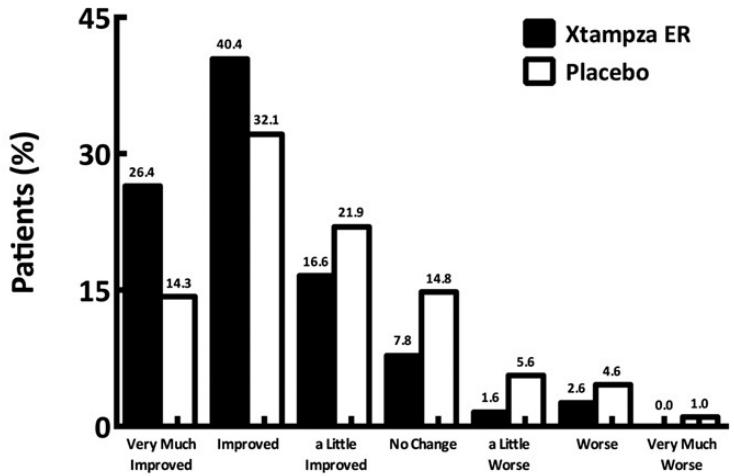
Gimbel J, Spierings ELH, Katz N, Xiang Q,Tzanis E, Finn A. PAIN157(11):2517-2526, November 2016.

Mean (SE) change from baseline in NRS pain intensity in double-blind treatment period (with imputed values)

(n=511, 54% of screened group)

Enriched Design Opioid Continuation

Moderate to Severe CLBP

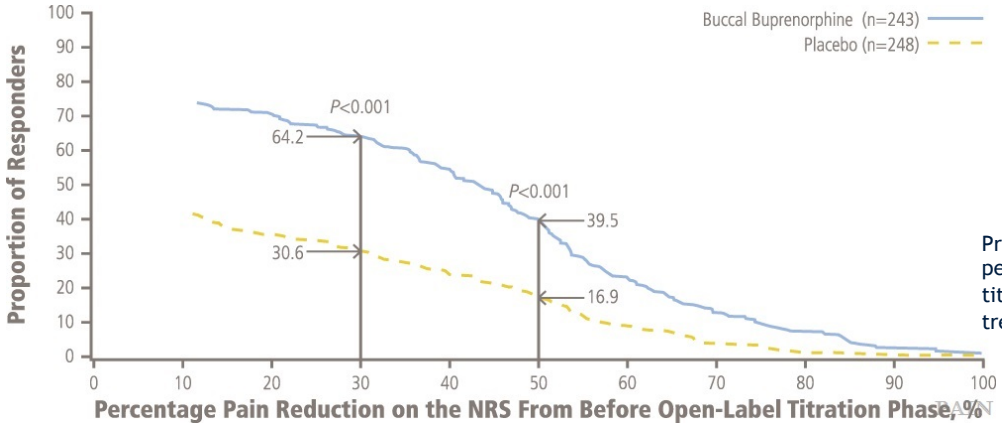


ER = extended-release

PAIN

Katz Nl, Kopecky EA, O'Connor M, Brown RH, Fleming AB. PAIN156(12):2458-2467, December 2015.

Patients' ratings of analgesic satisfaction at the final visit ($P < 0.0001$).



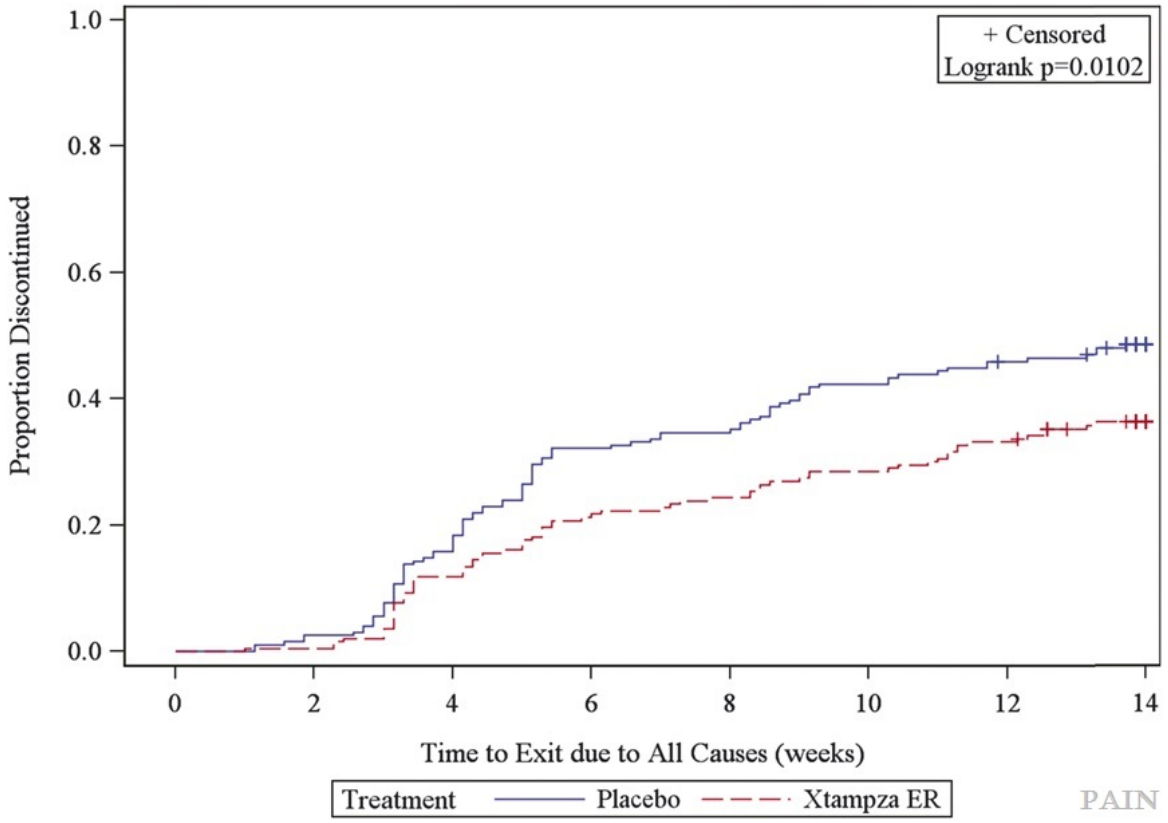
PAIN

Gimbel J, Spierings ELH, Katz N, Xiang Q,Tzanis E, Finn A. PAIN157(11):2517-2526, November 2016.

Proportion of responders with selected percentage pain reduction before open-label titration to week 12 in the double-blind treatment period.

Multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-sever chronic low back pain

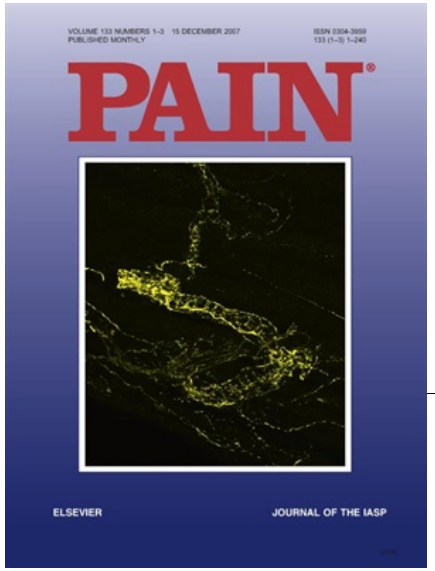
Katz, Nathaniel; Kopecky, Ernest A.; O'Connor, Melinda; Brown, Robert H.; Fleming, Alison B. (2015) PAIN156(12):2458-2467



Time-to-exit (all causes) from the study (P = 0.0102).

Summary Points
CLBP studies

- Carefully screened subjects (1/3 complete study)
- Lower pain intensity and greater satisfaction on drug
- Mean pain scores decline from @ 7/10 to 3/10
- SF36 gains on drug
- Less rescue pain med on drug
- Rigorous RCTs, peer-reviewed, expert PIs
- No data beyond 12 weeks
- Pharma funded



Cannabis in Peripheral Neuropathy (2007)

Pain 133 (2007) 210–220

PAIN

www.elsevier.com/locate/pain

Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]

[a] *Division of Neurological Science, University of Liverpool, Liverpool, United Kingdom*
[b] *Gartnavel General Hospital, Glasgow, United Kingdom*
[c] *Solihull Hospital, Birmingham, United Kingdom* [d] *York District Hospital, York, United Kingdom* [e] *University Hospital, Leuven, Belgium*
[f] *Castle Hill Hospital, Hull, United Kingdom*

Received 11 March 2007; received in revised form 21 August 2007; accepted 21 August 2007

Cannabis for Neuropathic Pain

Oral THC:CBD spray for neuropathic pain. Nurmikko, TJ, Serpell MG, Hoggart B, Toomey, PJ, Morlion BJ, Haines D. PAIN133(1):210-220, 2007.

- Neuropathic peripheral pain with allodynia*
- 125 subjects pain > 4/10, 20% had prior cannabis use
- 5-week RCT parallel design, multi-center (UK, Belgium)
- Oro-mucosal THC:CBD spray SUD, past cannabis use allowed
- Psych DO other than depression excluded
- Established opioids continued
  - 12% on strong opioid, 57% on weak opioid
- Non-opioid adjuvants and analgesics continued
  - TCA 30%, AED 34%, NSAID 20%, Other Analgesic 13%
- Pharma supported

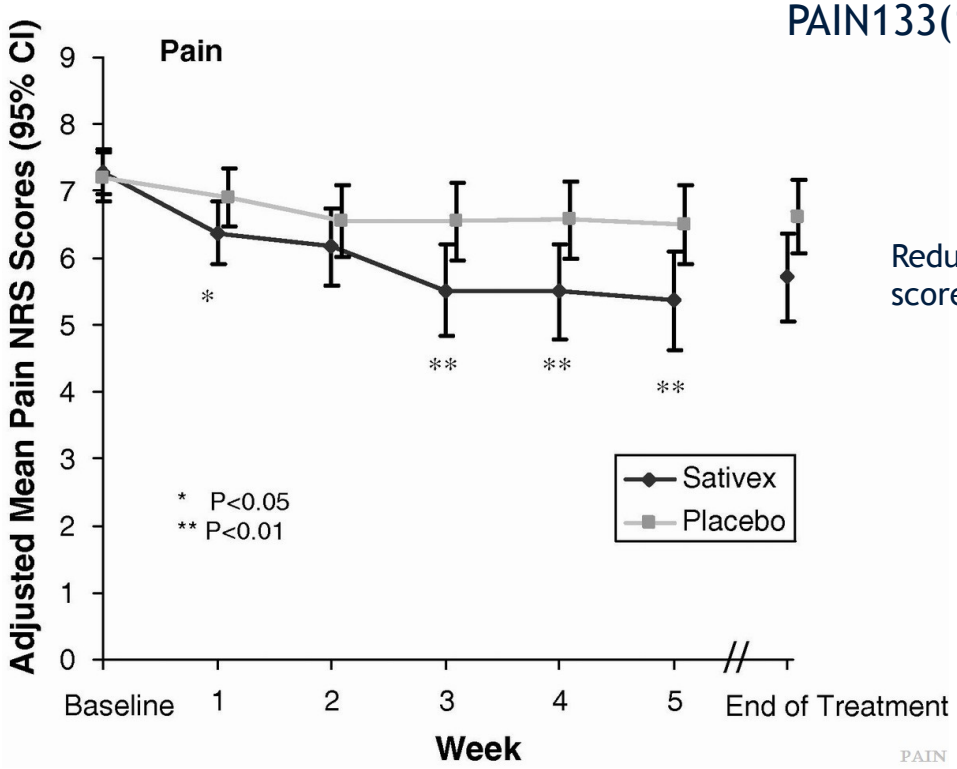
Sativex Outcomes

- Improved pain (p .007)
- Improved allodynia static and dynamic (p .02-.04)
- Improved sleep disturbance NRS (p .001)
- Improved disability Score PDI (p .003)
- GHQ 12 score NS
- Patient satisfaction with pain reduction (p < .001)
- 79% on Sativex, 89% placebo subjects complete

Oral THC:CBD spray for neuropathic pain. Nurmikko, TJ, Serpell MG, Hoggart B, Toomey, PJ, Morlion BJ, Haines D. PAIN133(1):210-220, 2007.

Sativex for neuropathic pain (2007)

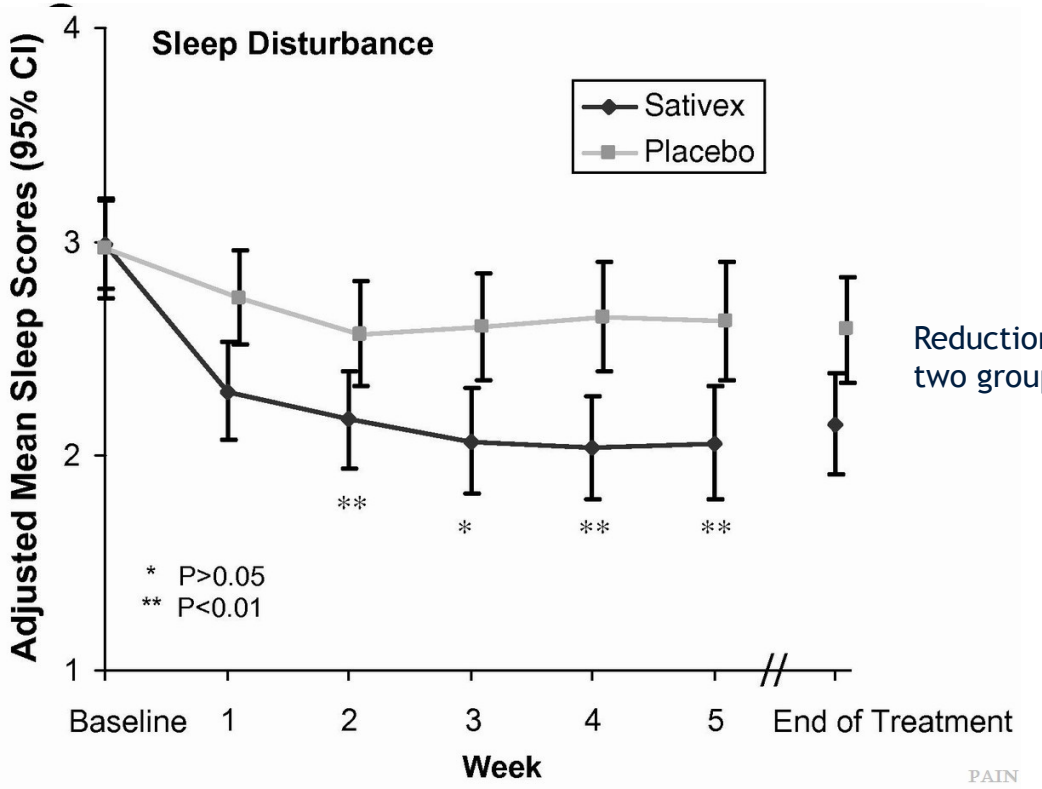
Nurmikko, TJ, Serpell MG, Hoggart B, Toomey, PJ, Morlion BJ, Haines D. PAIN133(1):210-220, December 2007.



Reduction of global neuropathic pain NRS scores in the two groups during the trial.

Sativex for neuropathic pain (2007)

Nurmikko, TJ, Serpell MG, Hoggart B, Toomey, PJ, Morlion BJ, Haines D. PAIN133(1):210-220, December 2007.



Reduction is sleep disturbance scores in the two groups during the trial.

Adverse Events on Sativex

- 91% subjects on sativex report at least one AE.
- Most frequent AEs were CNS or GI.

Adverse event	Number (%) of patients experiencing AEs	
	Sativex ($N = 63$)	Placebo ($N = 62$)
Dizziness	18 (28.6)	9 (14.5)
Nausea	14 (22.2)	7 (11.3)
Fatigue	13 (20.6)	5 (8.1)
Dry mouth	11 (17.5)	3 (4.8)
Vomiting	8 (12.7)	3 (4.8)
Feeling drunk	6 (9.5)	1 (1.6)
Headache	6 (9.5)	9 (14.5)
Diarrhoea	4 (6.3)	0
Nasopharyngitis	4 (6.3)	2 (3.2)
Anorexia	4 (6.3)	0
Somnolence	4 (6.3)	1 (1.6)
Abdominal pain upper	3 (4.8)	1 (1.6)
Disturbance in attention	3 (4.8)	0
Memory impairment	3 (4.8)	0

Nurmikko, TJ, Serpell MG, Hoggart B, Toomey, PJ, Morlion BJ, Haines D. PAIN133(1):210-220, December 2007.

Steps forward…

- Use opioids and cannabis for CNCP in carefully screened closely followed patients and cautiously
- Educate clinicians and trainees in evaluating trials
- Incentivize long-term studies
- Increase NIH support for high-quality clinical trials
- Reconsider DEA Schedule I status
- Improve state dispensary system
- Increase coverage for multidisciplinary treatment of CNCP [6]

[6]Gross J, Gordon DB. The strengths and weaknesses of current US policy to address pain. Am J Public Health 2019;109(1):66–72.

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