Opioid Combinations, Multi-Receptor Approaches to Analgesia

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Introduction

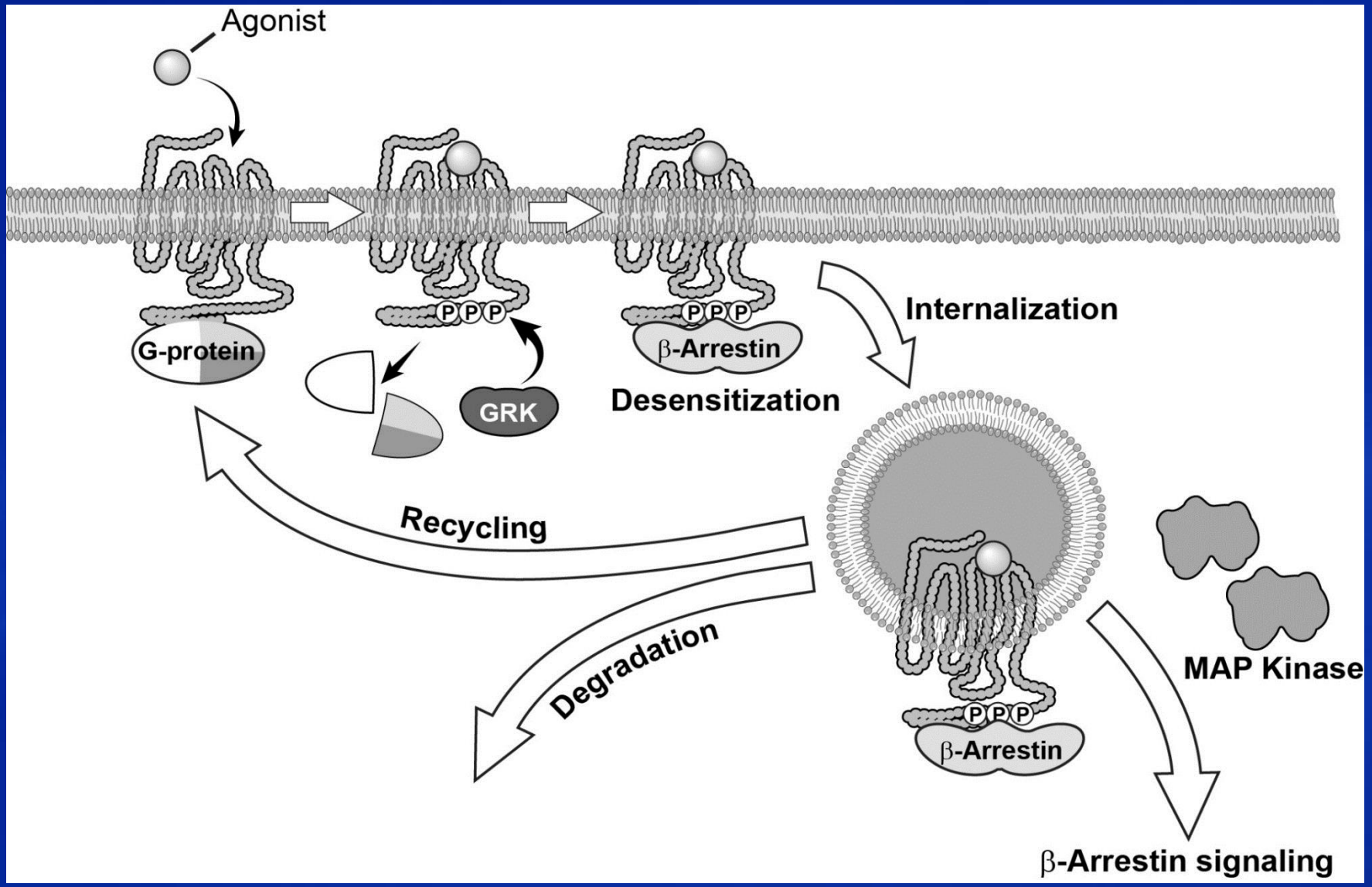
- Single opioid analgesics are modestly effective but have a narrow therapeutic index
- NNT is 3 for the most potent opioids
- Opioids produce analgesia through interactions with three major GPCRs: μ, d and k
- Multiple distinct opioid receptor subtypes have been described

Individual Receptors

- Analgesia occurs whether activating mu, kappa, delta and nociceptin (NOP) receptors
- Each have unique side effects
  - -mu- respiratory depression, constipation
  - -kappa-dysphoria, diuresis
  - -delta-seizures

Individual Benefits

- Kappa- blocks opioid and renal failure related pruritus, no respiratory depression
- Delta- lack of physical dependence, anxiolytic and antidepressant effect


Agonist
G-protein
P P P
GRK
β-Arrestin
Desensitization
Internalization
Recycling
Degradation
MAP Kinase
β-Arrestin signaling

Receptor Subtypes

- A single μ receptor gene generates multiple μ receptor subtypes through splicing of mRNA derived from the four major exons (7TM,6TM and 1TM)
- Opioids from different classes produce different physiologic effects through unique conformational receptor changes

Complexities in Analgesic Designs

- Multiple neurotransmitters and receptors in the pain pathway
- Pleiotropic functions of any single receptor and transmitter which dictate “lateral” benefits (dyspnea) and emerging toxicity (constipation)
- Receptor intrinsic efficacy and biased signaling between G-proteins, beta-arrestin, kinases
- Allosteric modulator (receptor “facilitator” without activating the receptor) or orthosteric activator
- Heterodimer interactions

Complexities in Analgesic Designs

- Receptor subtypes-Mu 7-TM, 6-TM, kappa 1-3
- Solubility and penetration into the CNS
- Bioavailability

Gunther T 2017

Circumventing Opioid Side Effects

- Targeting opioid receptor subtypes-IBNtxA and 6-TM receptors
- Bias signaling to G-protein signaling- triazole analogues and kappa receptors

Lu Z 2015

Wieskopf J 2014

Lovell K 2015

Selective Biased Signaling Opioid ; TRV-130

Background TRV-130

- Morphine analgesia is enhanced by knockdown of beta-arrestin
- Morphine respiratory depression and constipation are reduced by beta-arrestin knock
- Beta-arrestin negatively modulates analgesia and positively modulates respiratory depression and constipation

TRV-130

- Biased ligand which activates G-proteins and fails to activate beta-arrestin
- Stabilizes the mu receptor conformation which favors G-protein signaling and minimizes beta-arrestin / receptor interactions

TRV-130 Preclinical

- 400-fold mu receptor selectivity vs. kappa and delta receptors
- 10-fold more potent analgesic in mouse models than morphine
- Quicker onset to analgesia
- Equianalgesic doses with morphine produces much less respiratory depression than morphine
- Respiratory depression (severe) not seen at 8-fold equianalgesic doses
- Less adverse effect on GI transit

TRV-130 Clinical

- Healthy volunteers
- Compared to morphine 10mg IV
- TRV-130-3 and 4.5mg
- TRV-130 had greater analgesia
- TRV-130 had less adverse effect on respiratory drive
- Less nausea with TRV-130

Soergel D. Pain 2014

Heterodimers

- Spontaneously arise
- Dictate trafficking
- Changes G-protein signaling, change in bias signaling
- Alter the pharmacologic properties on individual monomers

Approaches to Targeting Multiple Receptors

- Drug cocktails
- Multiple ligands with a linker designed for heterodimers
- Single chemical entity which binds distinct receptors such as buprenorphine (Mu/NOP), nalbuphine (Mu antagonist/Kappa agonist)
- Single chemical entity which binds opioid receptor to transporter (tapentadol, tramadol)

Mu and Delta Agonist

- Targets inflammatory and neuropathic pain more than acute pain due to progressive dimer formation
- Lowers morphine analgesic tolerance
- Antidepressant activity

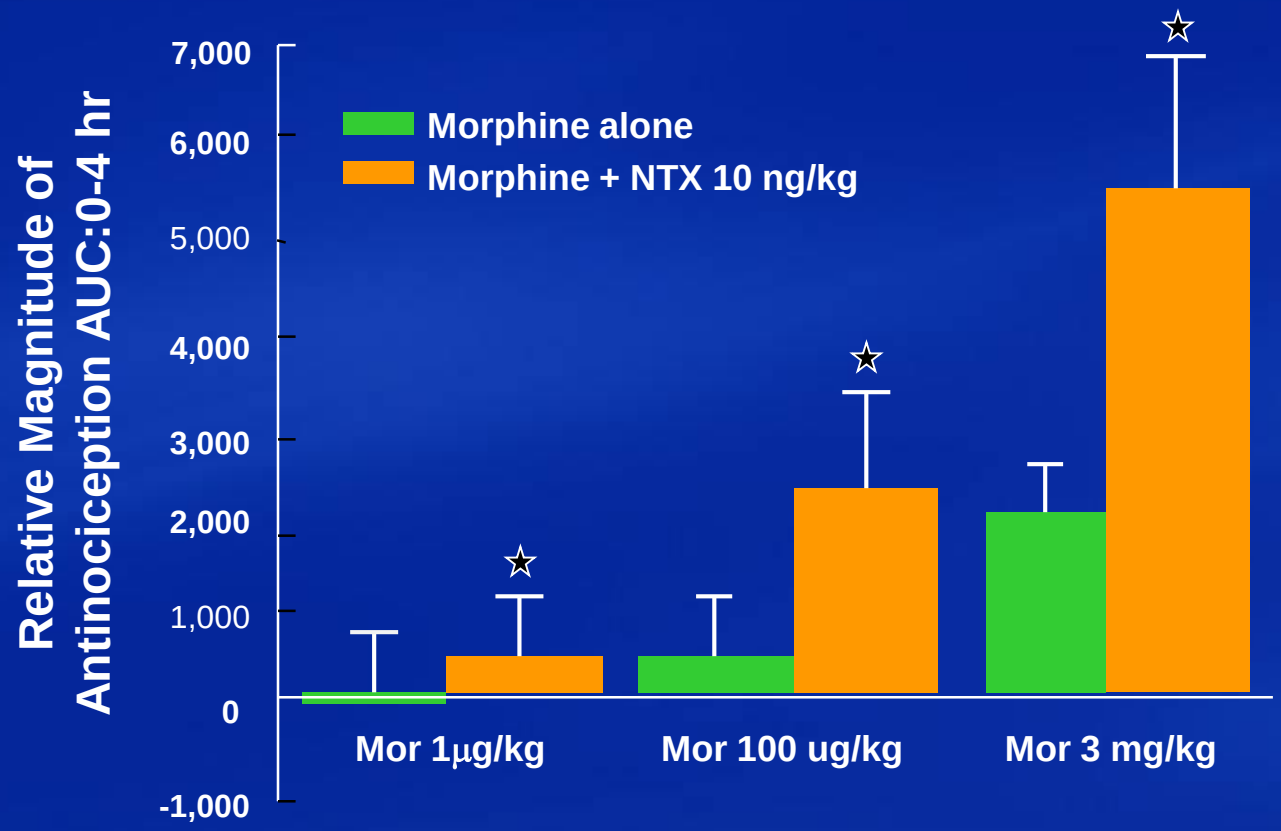
Cahill C 2003

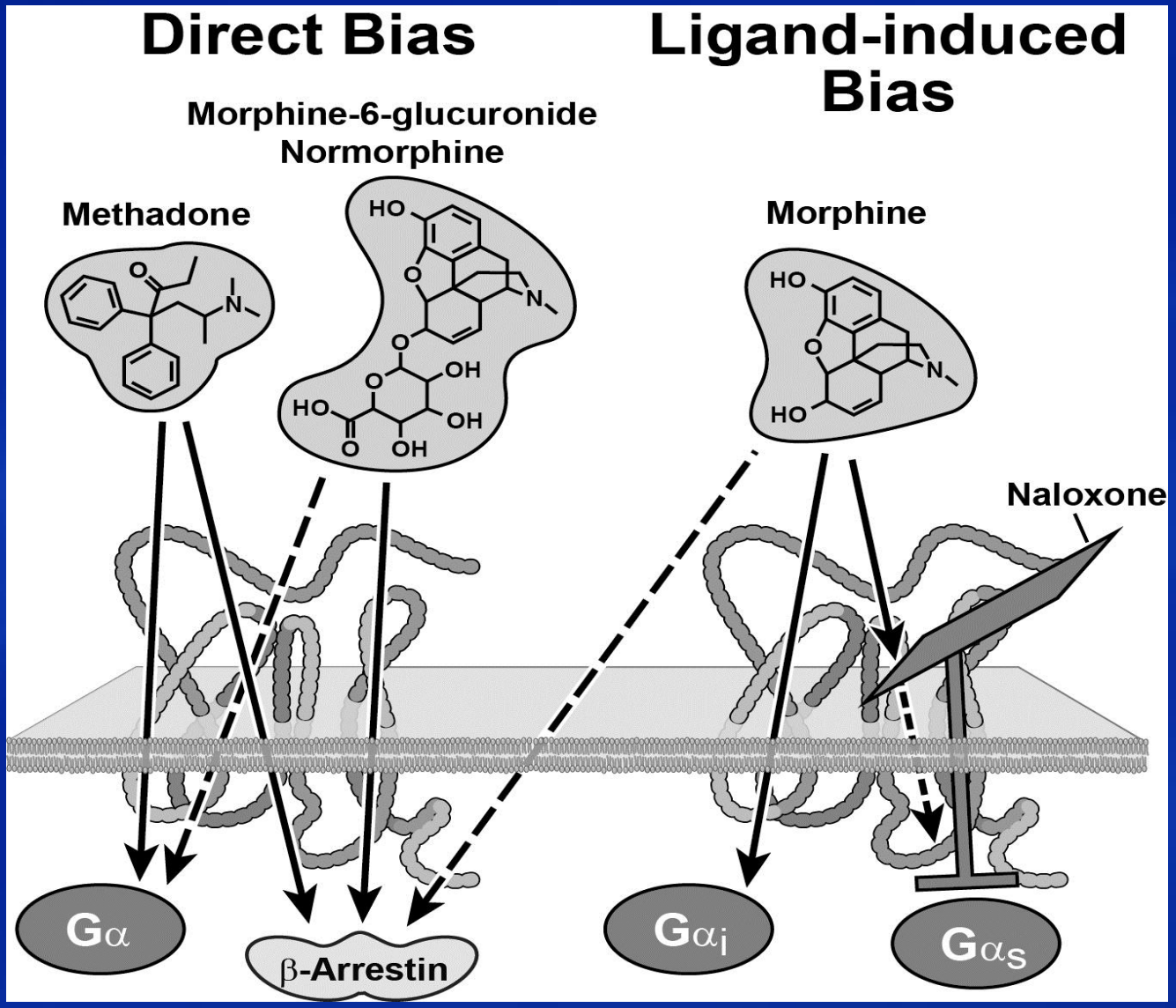
Balboni G 2010

Agonist and Antagonist Combinations

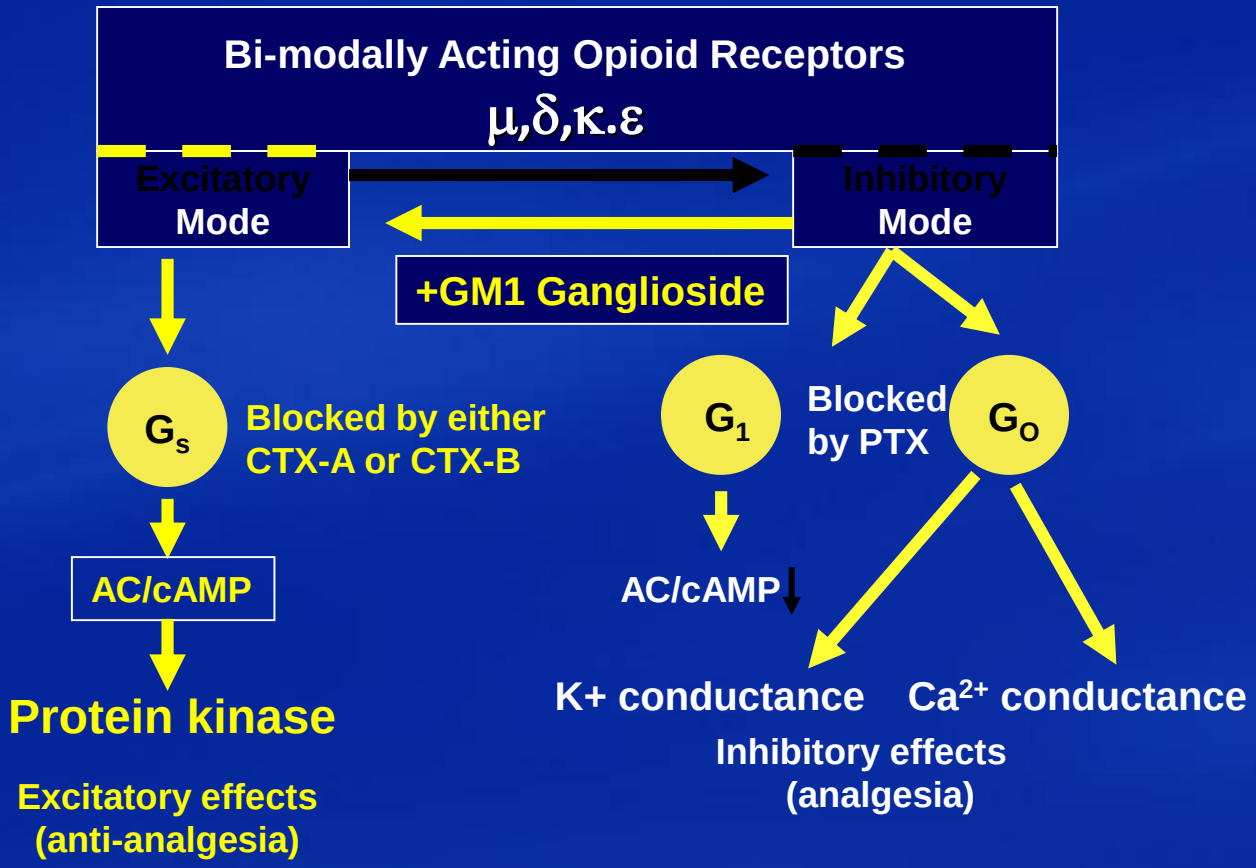
Agonist and Antagonist Combinations; Preclinical

- Premedication with ultra-low dose naloxone prior to morphine causes a left-shift morphine response in animal models


Relative Magnitude of Antinociception AUC:0-4 hr
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
-1,000
Morphine alone
Morphine + NTX 10 ng/kg
Mor 1μg/kg
Mor 100 ug/kg
Mor 3 mg/kg


Direct Bias
Ligand-induced Bias
Morphine-6-glucuronide
Normorphine
Methadone
Morphine
Naloxone
Gα
β-Arrestin
Gαi
Gαs

Bi-modal Opioid Modulation with Dose



Mu Agonist and Antagonist Combinations

- There may be a concern about the risk for addiction with combinations of agonists and antagonists
- Ultra-low dose naltrexone with morphine increases conditioned place preference compared with morphine alone in one animal study

Mu Agonist Delta Antagonist

- Ultra-low dose delta receptor antagonist plus μ receptor agonist augments antinociception and reduces physical dependence in animal models
- Synergy is selective; only certain delta receptor antagonists improve morphine antinociception
- A delta receptor antagonist such as naltrindole with morphine prevents dimer destruction

Mu Agonist Delta Antagonist

- Antinociceptive synergy between μ agonists and delta antagonists are reported in animal models; the delta receptor does not need to be activated (MDAN-oxymorphone/naltrinadole)
- Combinations cause a dose-dependent left-shift in response curves

Mu Agonist Delta Antagonist: Preclinical

- Concentrations of delta antagonists at the receptor site is critical to synergy
- Bimodal cooperation between ligands occurs with low doses of delta antagonists and is lost at higher doses
- Barrier to clinical development

Kappa Agonist / Mu Antagonists

Nalbuphine

- Reverses respiratory depression of both IV and spinal opioids
- 3 mg blocks pruritus from spinal morphine

Moldenhauer C 1985

Penning J 1988

Somrat C 1999

Comparisons of Nalbuphine with Morphine for Analgesic Effects and Safety: Meta-analysis of Randomized Controlled Trials

Zeng and colleagues
Scientific Report 2015

Nalbuphine vs. Morphine

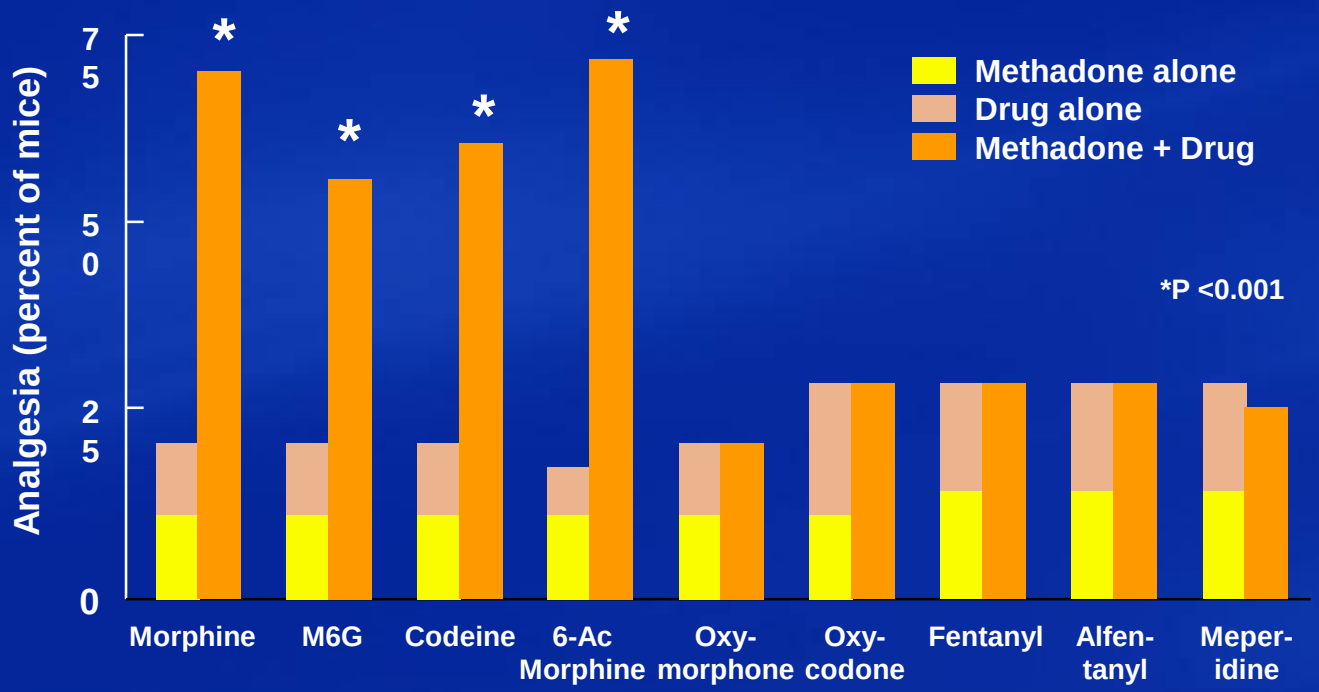
- 10 moderate to high quality trials
- 620 patients
- Bayesian analysis using credible intervals
- Pain relief; 1.1 (95% CI 0.67-1.63)
- Results confirmed on sensitivity analysis

Nalbuphine vs Morphine Safety

- Nausea RR 0.78 (95% CI 0.6-0.99)
- Vomiting RR 0.65 (95%CI 0.5-0.85)
- Pruritus 0.17 (95% CI 0.09-0.34)
- Respiratory depression 0.27 (95% CI 0.12-0.57)
- No significant steady heterogeneity

Zeng 2015

Morphine and Methadone


Analgesia (percent of mice)
7
5
5
0
2
5
0
*
*
*
*
Methadone alone
Drug alone
Methadone + Drug
*P <0.001
Morphine
M6G
Codeine
6-Ac Morphine
Oxy-morphone
Oxy-codone
Fentanyl
Alfen-tanyl
Meper-idine

Methadone as a Co-analgesic: Systematic Review

Adverse affects with the combination

- 90% had adverse reactions
- Drowsiness 50%
- Confusion 27%
- Nausea 20%
- Myoclonus 16%
- Missing data, attrition and no randomized trials

Courtemanche F 2016

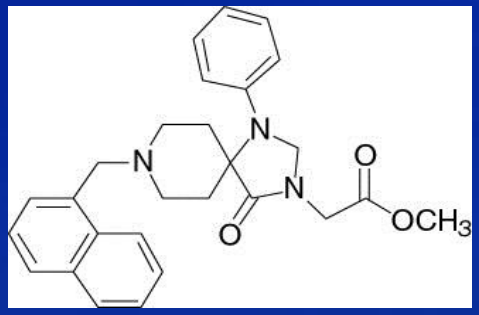
Nociceptin Mu Bifunctional Ligands

Nociceptin

- Spinal analgesia but by ICV route hyperalgesia
- Low dose-anti-opioid and hyperalgesia
- High dose-analgesia
- Targets chronic neuropathic pain > acute nociceptive pain

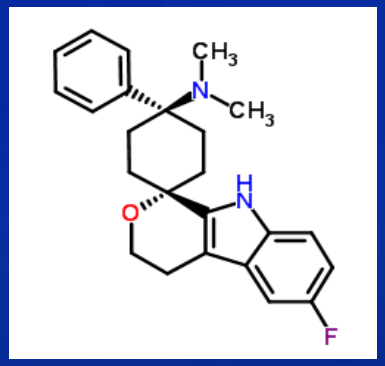
King M 1997

Mogil J 2001



Cebranopadol

- Full mu agonist, nearly full kappa agonist, NOP agonist
- Broad analgesic activity in animal models- acute, inflammatory, neuropathic and cancer pain
- Reduced motor and respiratory toxicity even at high doses
- Better tolerated than other opioids
- In phase III trials



Linz K 2014

Rizzi A 2016

Rationale for Mu Agonist NOP Antagonist

- Prolong mu agonist exposure upregulates substance P and NOP receptors leading to analgesic tolerance
- NOP receptor antagonist reduces substance P and pain in neuropathic animals treated with morphine

Longmore J 1997

Gonzalez M 2000

KGNOP1- Mu Agonist NOP Antagonist

- Reduced neuropathic hyperalgesia 4000-fold greater than tramadol and 35-fold greater than morphine in animals
- Anti-neuropathic pain/antinociceptive to respiratory effects revealed that KGNOP1 was safer than tramadol (ED50 ratio: 5.44×10^{-3} vs 0.24) and morphine (ED50 ratio: 0.72 vs 1.39)

Lagard C 2017

Summary

- It is unlikely that combining commercially available opioids in combination will have a major clinical outcome
- Advancement in basic opioid pharmacology has lead to important avenues to analgesic development
- Targeting certain opioid receptor subtypes, developing G-protein biased opioid ligands and development of multitargeted analgesics may improve the therapeutic index of standard opioids.

Opioid Induced Hyperalgesia

Mellar P Davis MD, FCCP, FAAHPM

Introduction

- Repeated administration of morphine in
  - Animals causes physical tolerance, dependence and neuropathic hyperalgesia
- Relationship between pain intolerance and the rewarding effects of opioids
- Nature versus nurture
  - Conditioned response
  - Genetic predisposition

Mao J., 1995
Frischknecht H., 1988
Elmer G., 1995, 1998

Opioid Induced Hyperalgesia (OIH)

1. How consistently does OIH occur?
2. Is OIH modality (pain) specific?
3. Is OIH opioid specific or duration related?
4. Is there an association between OIH and opioid analgesic tolerance?
5. Is OIH a laboratory finding or doesn't have clinical relevance?
6. Is there an association between OIH and gender, age or addiction?

Terms

Detection of Stimuli

Pain thresholds

Pain tolerance-duration

Unpleasantness

Temporal summation

Conditioned pain modulation

Quantitative Testing

Heat threshold
Cold threshold
Thermal pain
Cold pressor tolerance
Electrical stimulation pain
Punctate mechanical pain
Pressure pain
Change from thermal thresholds to thermal pain
Wind up – temporal summation
Conditioned pain modulation
Pain and unpleasantness to local anesthetics

GAPs in Understanding

- Studies used difference quantitative sensory testing
- Heterogeneous populations
  - Maintenance therapy
  - Chronic pain
  - Post operative pain
  - Cancer pain
- Different opioids, doses and adjuvants
- Chronic pain and addiction may be associated with pain sensitivity, pain tolerance or unpleasantness
- Timing of testing to opioid dose

Mechanisms

- Upregulation of NMDA receptors and neurotransmission
- Upregulation of substance P and CGRP
- Upregulation of CCK within the rostroventromedial medulla
- Upregulation of spinal dynorphin
- Reduced modulation of pain through subnucleus reticularis dorsalis and CPM (DNIC)
- Upregulation of 6-transmembrane mu receptors

Cold Pressor Pain

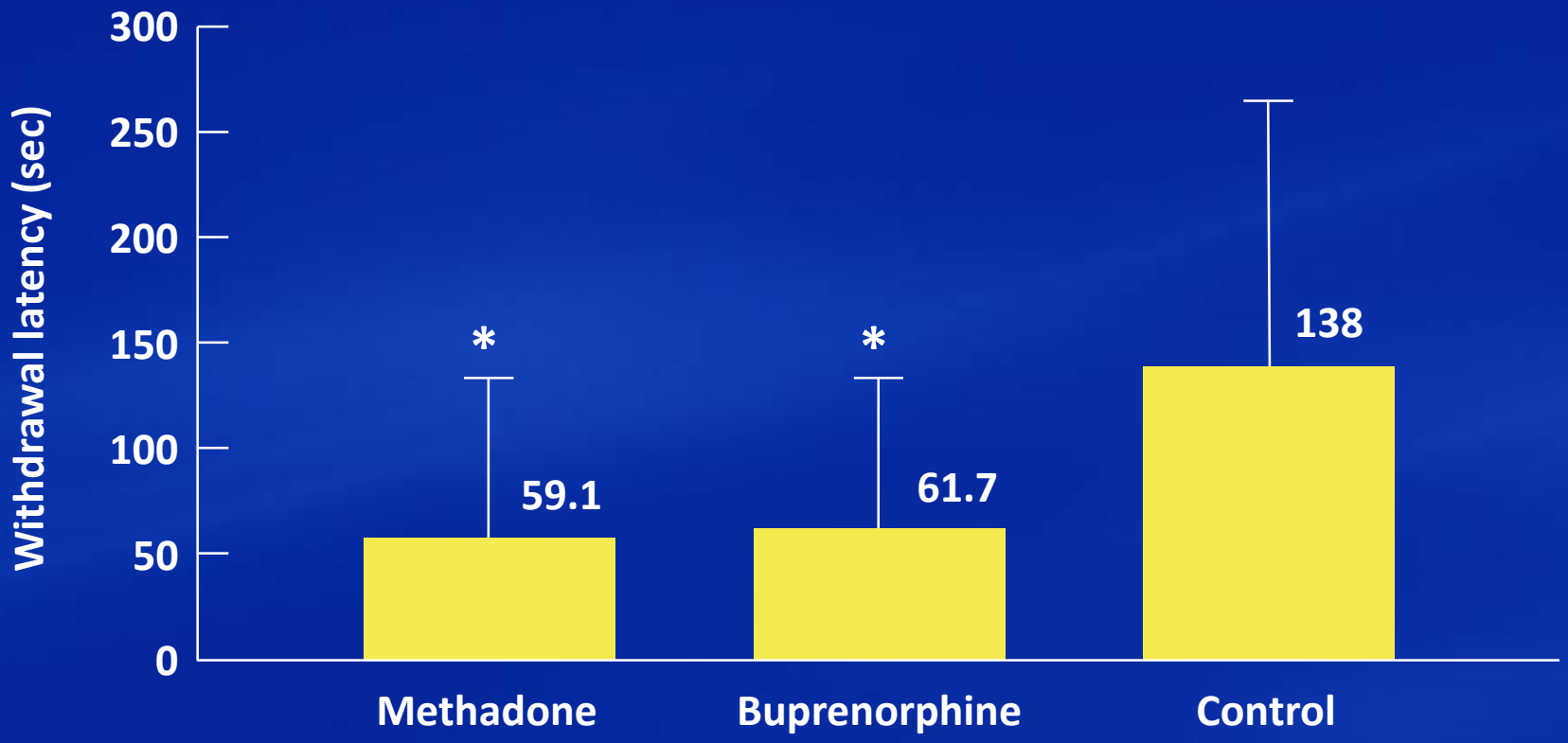
Pain Intolerance in Opioid Maintained former Opiate Addicts: Effect of Long-Acting Maintenance Agent

Peggy Compton, V.C. Charuvastra, Walter Ling

Drug and Alcohol Dependence
2001; 63:139-146

Design:	3-group matching
Patients:	Methadone, buprenorphine, maintained addicts
Controls:	Community matched controls
Intervention:	Cold pressor tolerance
Outcome:	Cold tolerance

Results



Cold-pressor withdrawal latency in long-acting opioid-maintained former opioid addicts and matched controls. Each bar (and bracket) represents mean value (and SD) for the subjects derived from three testing sessions. Asterisk indicates significant ($P < 0.05$) difference from the control group.

Hyperalgesic Responses in Methadone Maintenance Patients

Mark Doverty, Jason White, Andrew Somogyi, et al. *Pain* 2001; 90:91-96

Design: 2 matched cohort

Patients: Methadone, maintained addicts

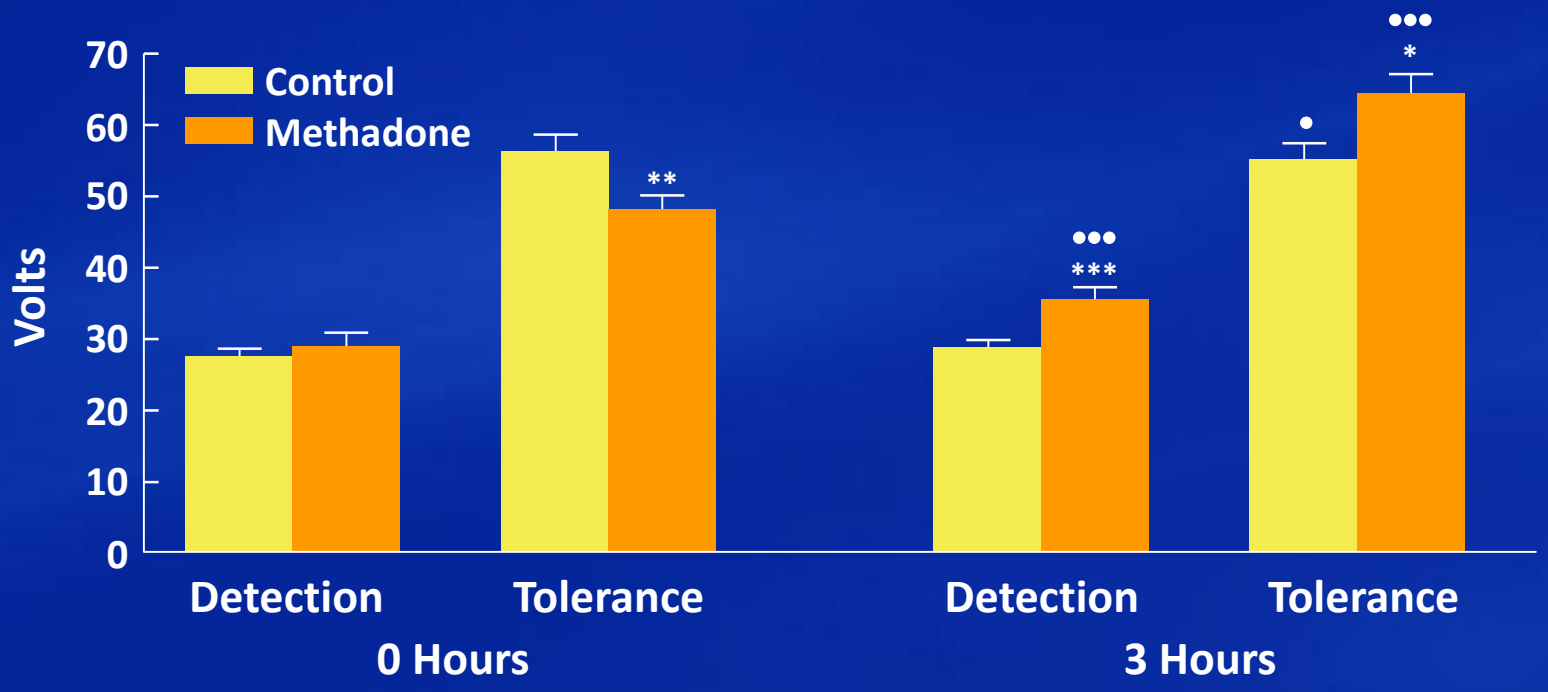
Controls: Matched healthy individuals

Intervention: Electrical stimulation pain, cold pressor test, methadone concentrations

Outcome: Pain tolerance and pain detection (ratios)

Results

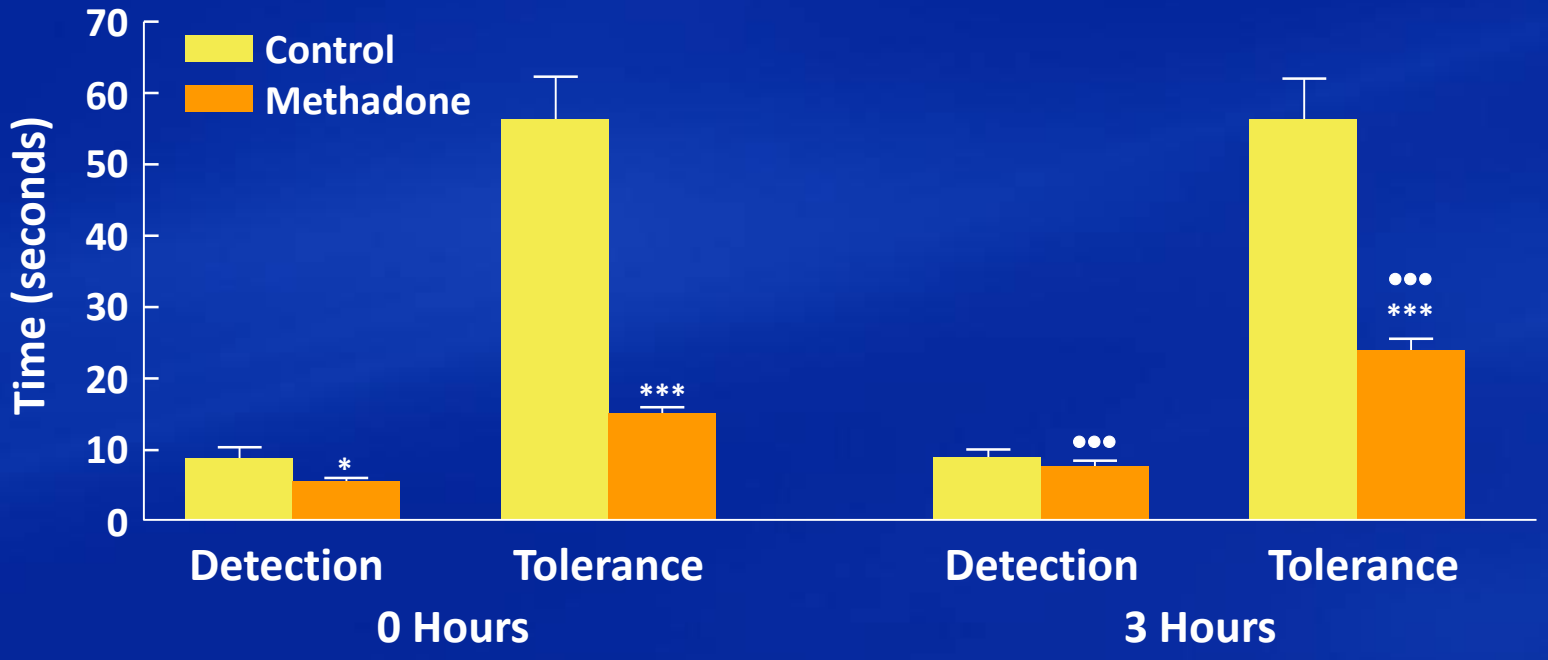
Electrical Stimulation



Comparison of mean (+SEM) pain detection and pain tolerance values at 0 and 3 h in 16 methadone maintenance patients and 16 matched controls. Methadone vs controls: 0 h, detection $P = 0.744$, tolerance $^{**}P = 0.013$; 3 h, detection $^{***}P = 0.002$, tolerance $^{*}P = 0.015$, 0 vs 3 h; methadone, detection $^{\bullet\bullet\bullet}P < 0.0001$, tolerance $^{\bullet\bullet\bullet}P < 0.0001$; controls, detection $P = 0.096$, tolerance, $^{\bullet}P = 0.018$.

Results

Cold Pressor Test



Comparison of mean (+SEM) pain detection and pain tolerance values at 0 and 3 h in 16 methadone maintenance patients and 16 matched controls. Methadone vs controls: 0 h, detection *P = 0.023, tolerance ***P < 0.0001; 3 h, detection P = 0.369, tolerance ***P < 0.0001, 0 vs 3 h; methadone, detection •••P < 0.0001, tolerance •••P < 0.0001; controls, detection P = 0.211, tolerance, P = 0.857.

Opioid Tolerance and Hyperalgesia in Chronic Pain Patients After One Month of Oral Morphine Therapy: A Preliminary Prospective Study

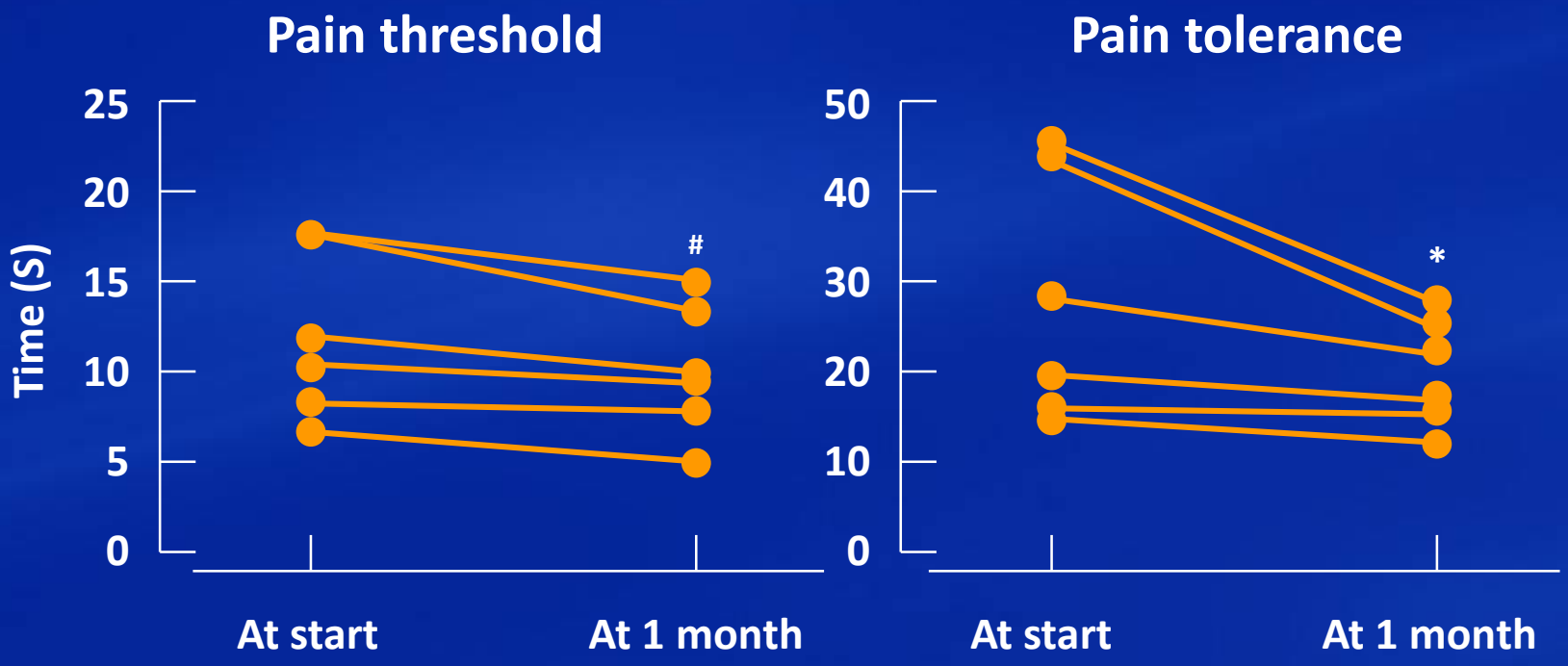
Larry Chu, David Clark, Martin Angst

Journal of Pain
2006; 7(1):43-48

Design:	Prospective observational study, pre-post sustained morphine
Patients:	Chronic low back pain (CLBP)
Controls:	Patient prior to opioid
Intervention:	Cold pressor test Heat pain test
Outcome:	Pain thresholds and tolerance
	Disability (Roland-Morris)
	Opioid withdrawal (OOWS)
	Remifentanil analgesia
	Morphine and metabolite levels

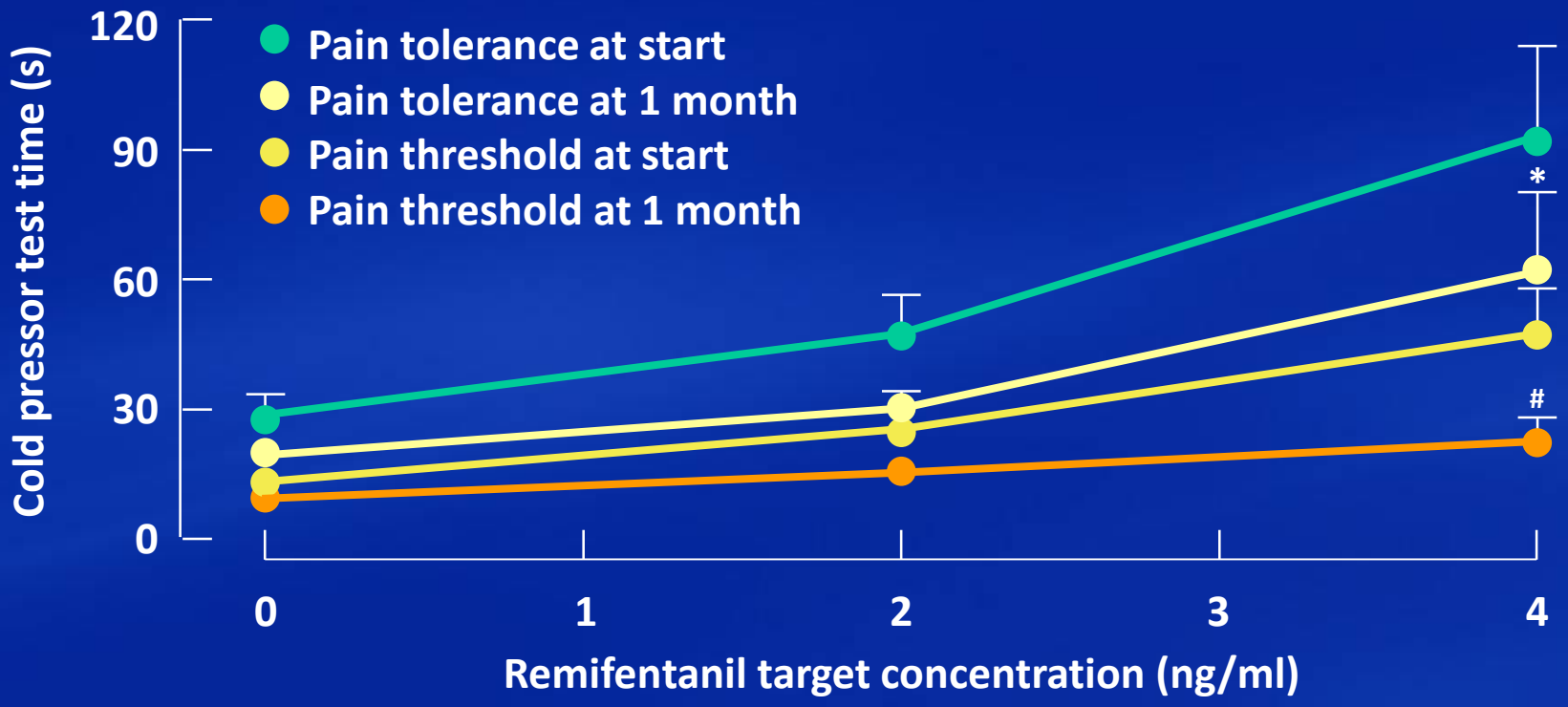
Results

Cold Pressor Test



The experimental pain threshold (time to first pain) and pain tolerance (time to intolerable pain) were assessed with aid of the cold pressor test before and 1 month after initiating chronic morphine therapy in 6 patients with chronic low back pain. The experimental pain threshold and pain tolerance were significantly decreased after 1 month of oral morphine therapy, indicating the development of opioid-induced hyperalgesia (paired *t* text. #pain threshold and *pain tolerance, $P < .01$)

Results



The remifentanil target plasma concentration vs analgesic response relationship was determined before and 1 month after initiating chronic oral morphine therapy in 6 patients with chronic low back pain. Analgesic effects were quantified with aid of the cold pressor pain test. The potency of remifentanil for increasing the experimental pain threshold (time to first pain) and pain tolerance (time to intolerable pain) was significantly decreased after 1 month or oral morphine therapy indicating the development of analgesic tolerance (mean ± standard error of the mean). Decreased potency was reflected statistically by a flattening of the slope or a right shift of individual plasma concentration vs analgesic response relationships (paired *t* test #pain threshold, $P = .03$; *pain tolerance $P < .01$).

Results

- Remifentanil target concentration versus analgesia
  - Reduced 47% - threshold
  - Reduced 49% - tolerance (figure 5)

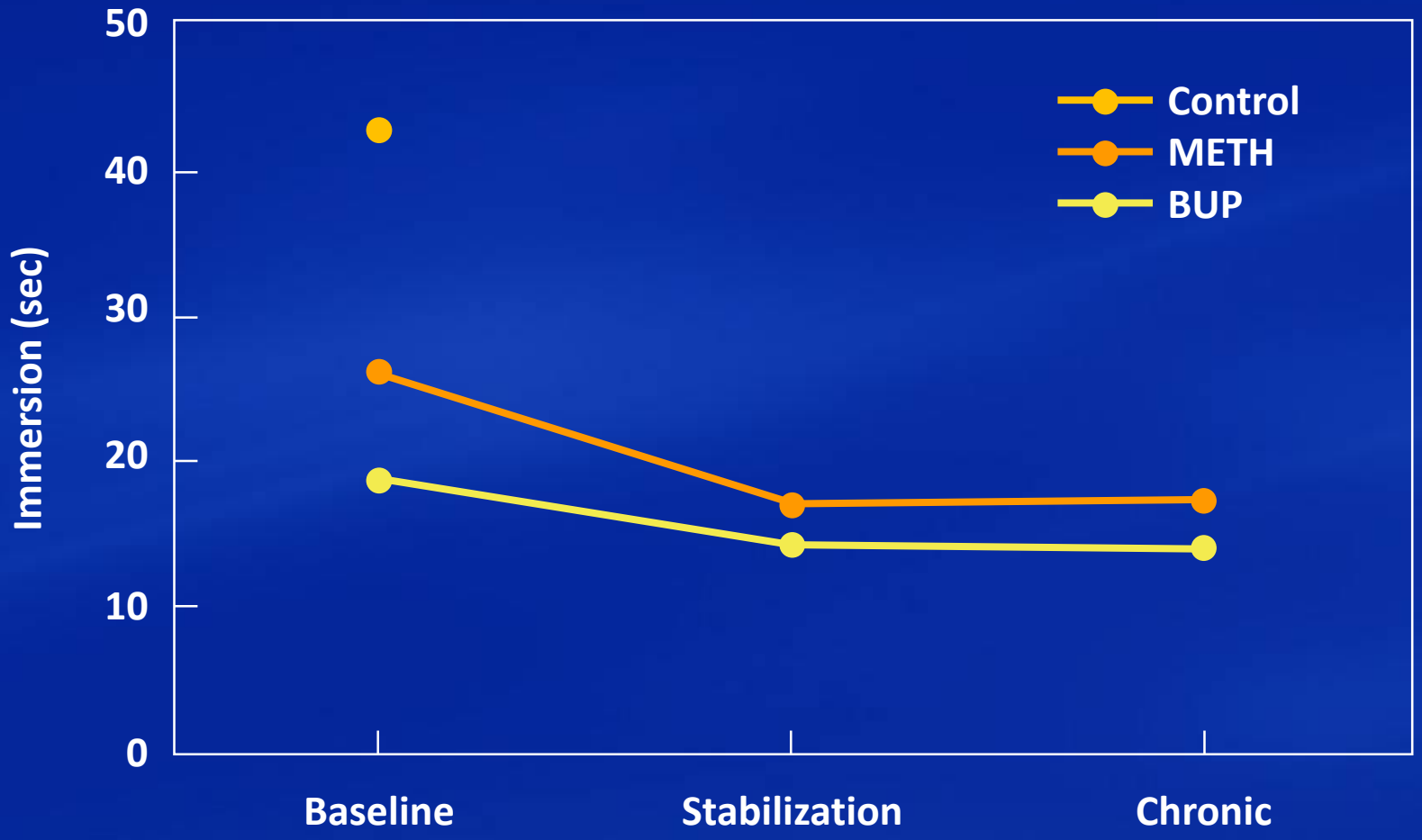
Hyperalgesia in Heroin Dependent Patients and the Effects of Opioid Substitution Therapy

Peggy Compton, Catherine P. Canamar, Maureen Hillhouse, et al.

Journal of Pain
2012; 4:401-409

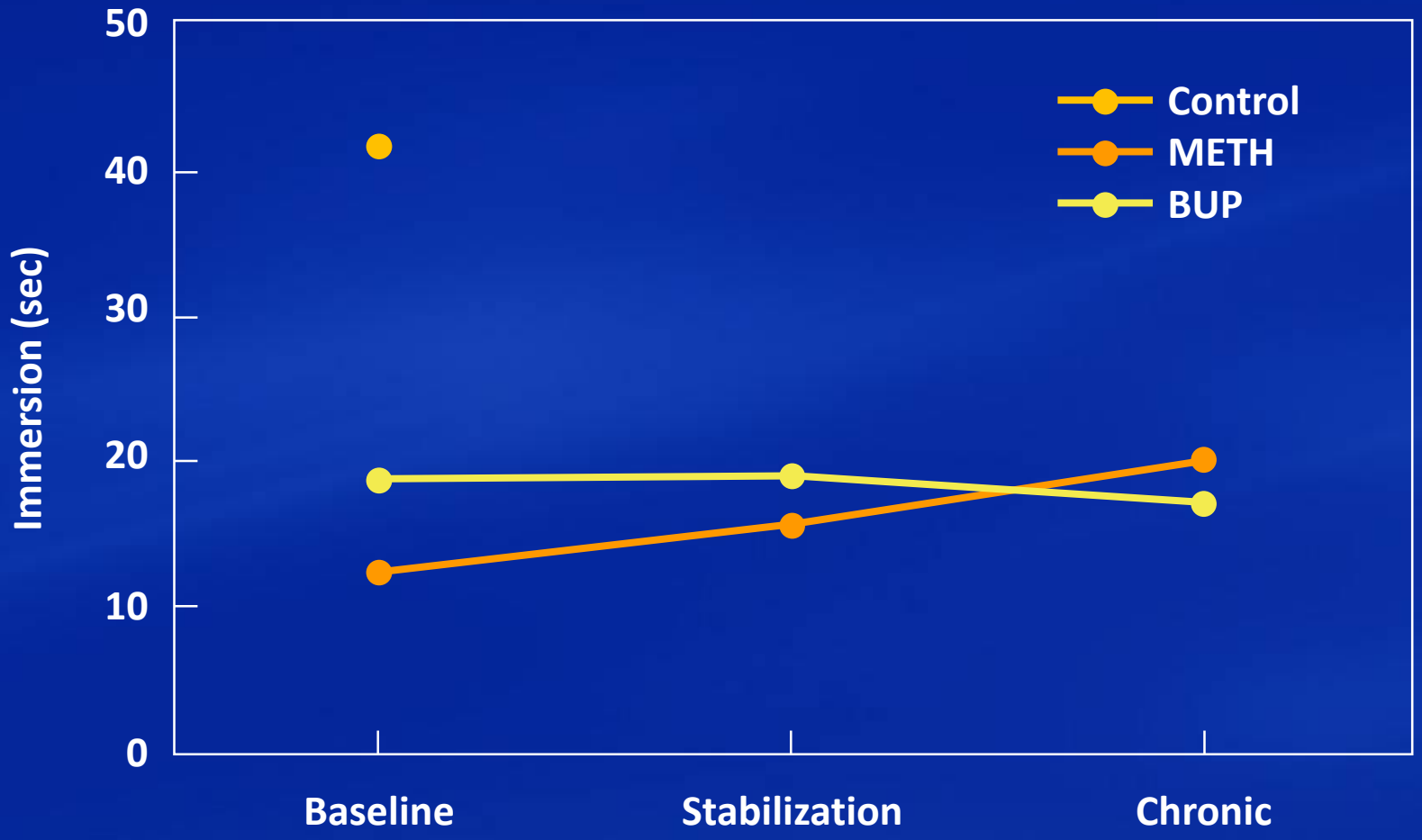
Design:	Survey, heroin addicts, and drug free controls
Patients:	Heroin addicts entering methadone or buprenorphine maintenance
Controls:	Drug-free individuals
Intervention:	Cold pressor test
	Electrical stimulation test
	12 weeks, 2 urine tests negative
Outcome:	Pain tolerance trough and preak
	at stabilization and 12 weeks

Results



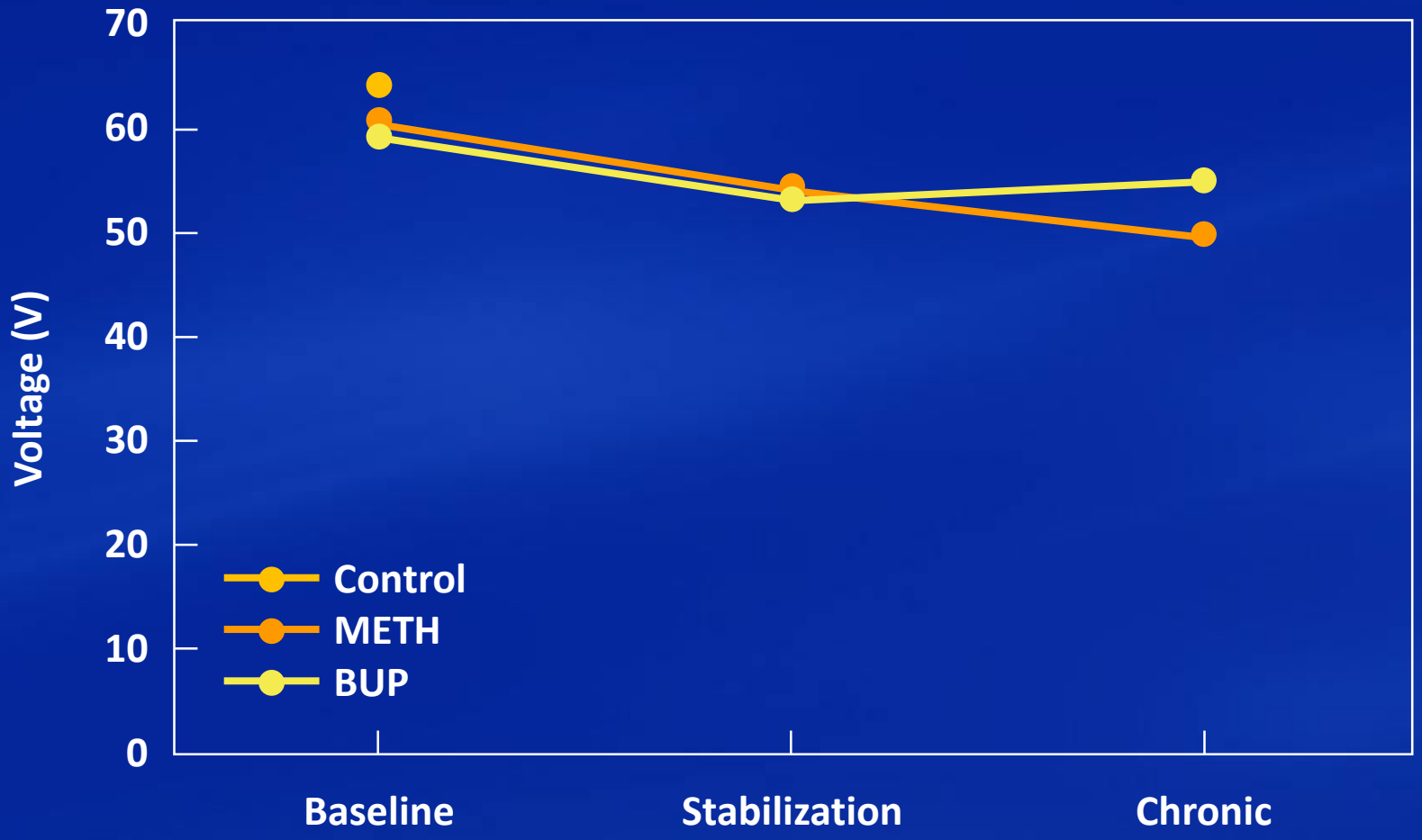
Cold-pressor pain tolerance (seconds) at trough medication plasma levels

Results



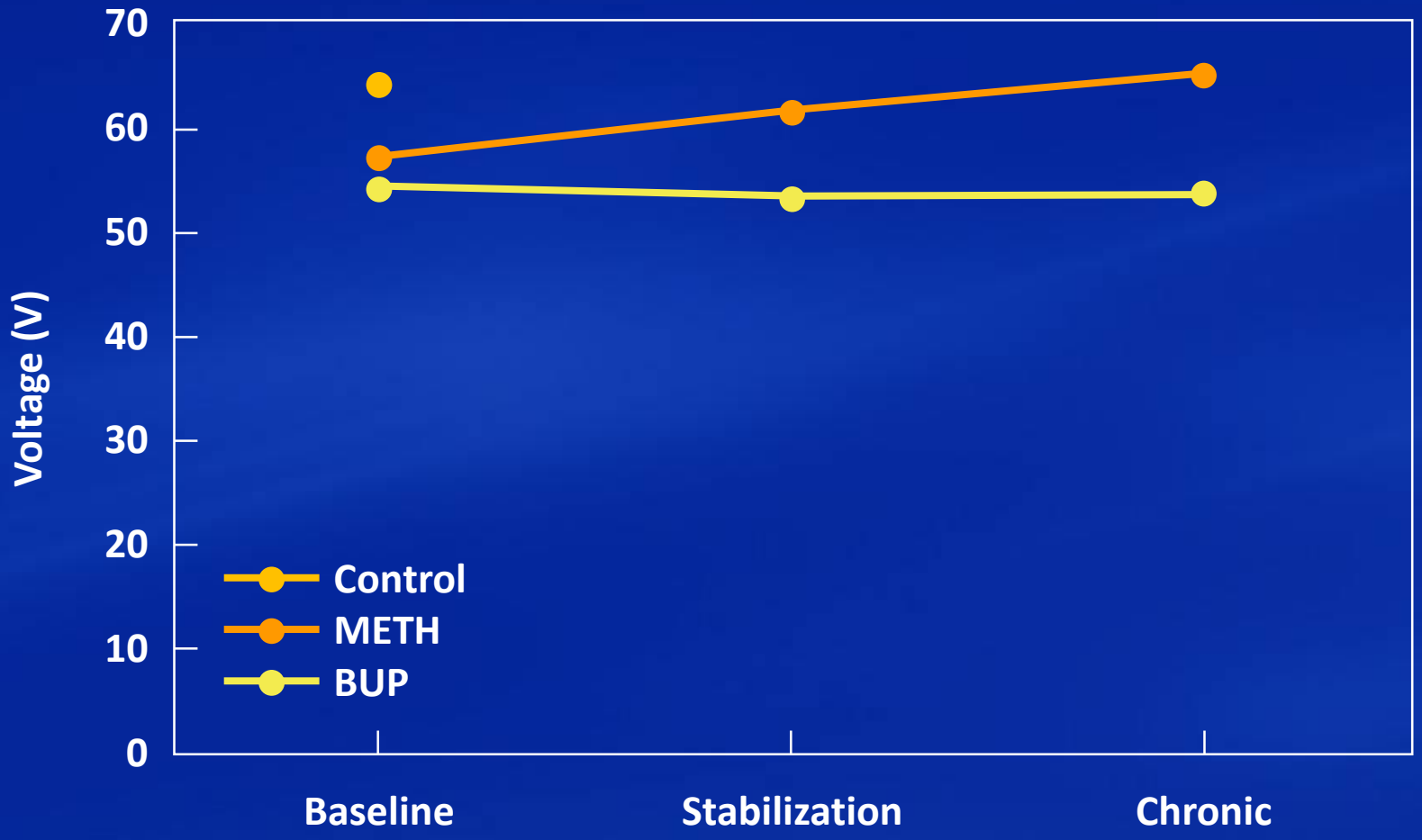
Cold-pressor pain tolerance (seconds) at peak medication plasma levels

Results



Electrical stimulation pain tolerance (volt) at trough medication plasma levels

Results



Electrical stimulation pain tolerance (volt) at peak medication plasma levels

Comparison of Pain Models to detect Opioid Induced Hyperalgesia

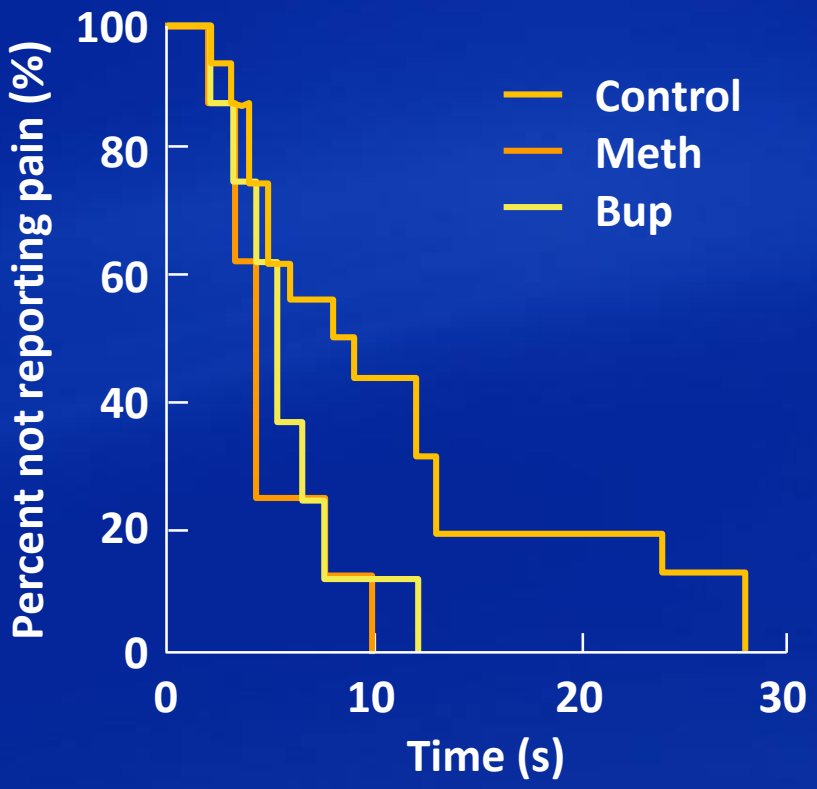
Sumithra Krishnan, Amy Slater, Thomas Sullivan

Journal of Pain Research
2012; 5:99-106

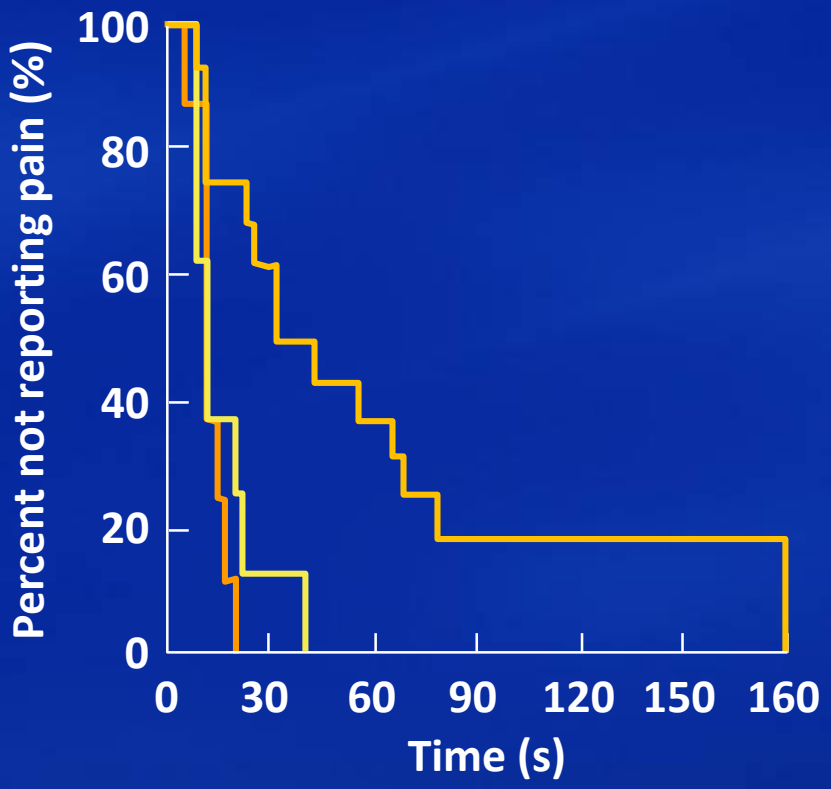
Design:	Comparison of buprenorphine and methadone maintained individuals with healthy controls
Patients:	Opioid dependent individuals
Controls:	Healthy matched controls
Intervention:	Cold pressor test
	Electrical stimulation test
	Mechanical pressure test
	Ischemic pain test
Outcome:	Pain thresholds and tolerance

Results

Cold pain threshold

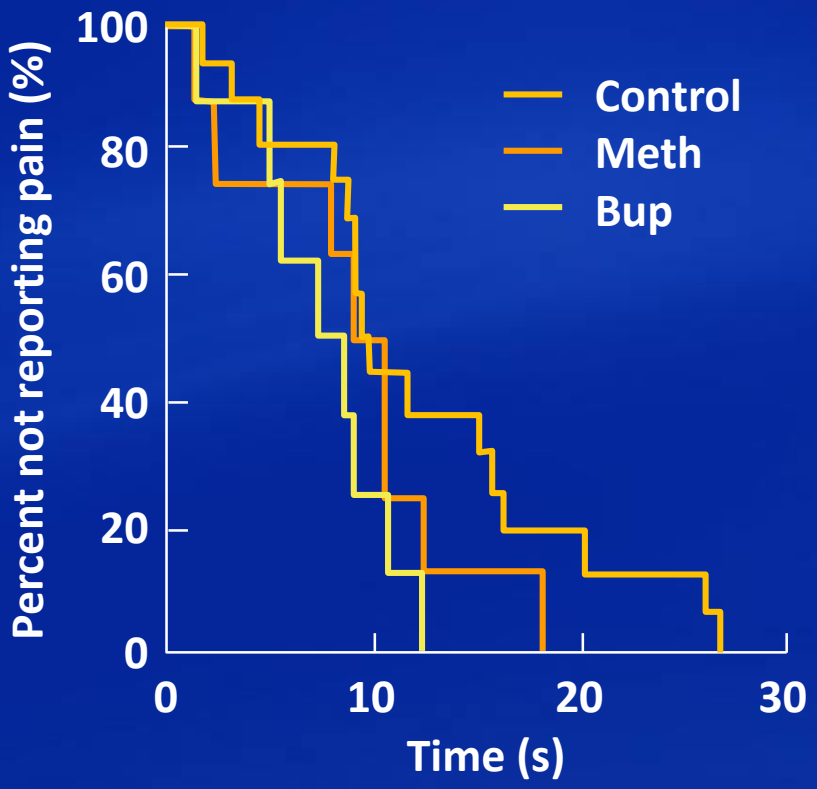


Cold pain tolerance

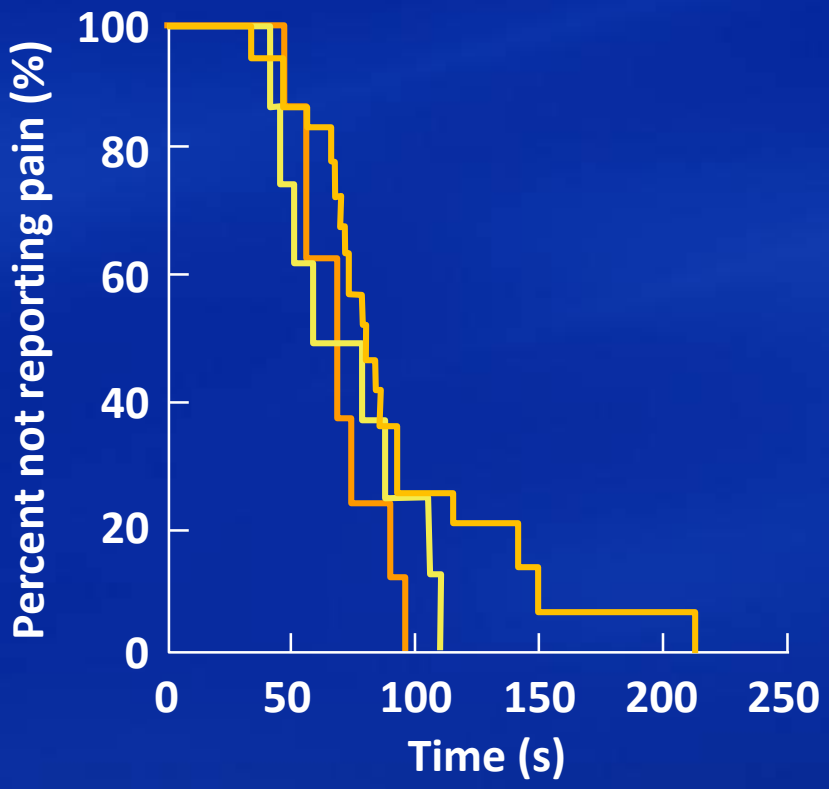


Results

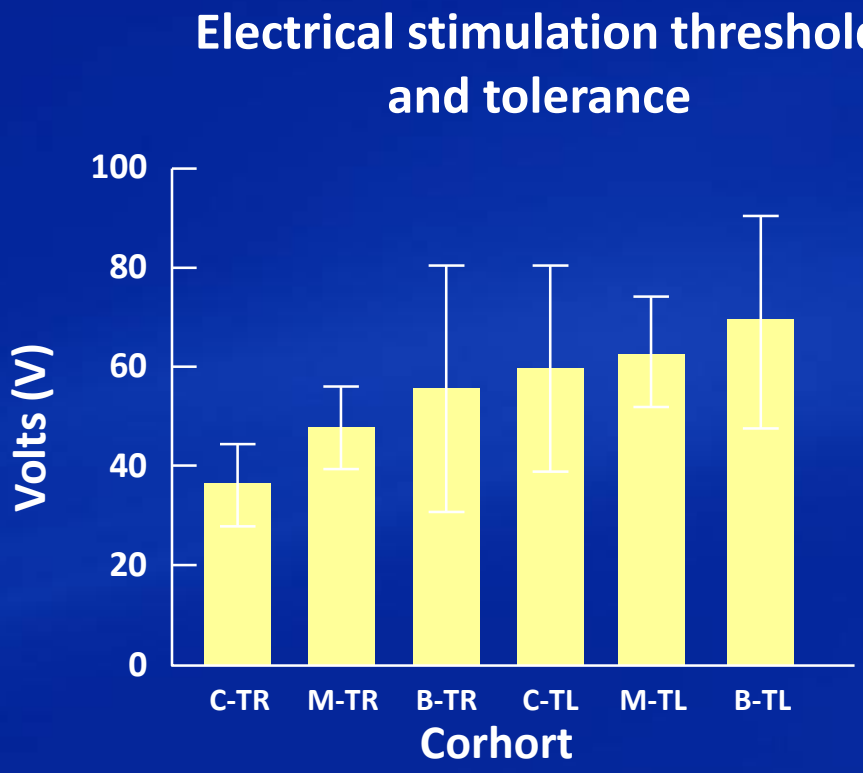
Ischemic pain threshold

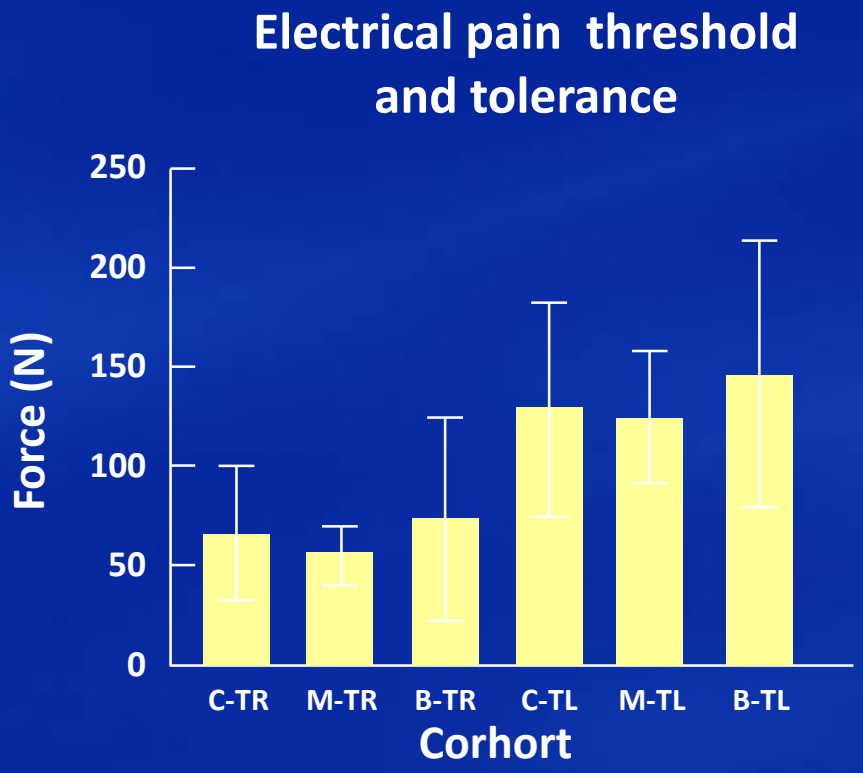


Ischemic pain tolerance



Results





Meth, methadone-dependent subjects; Bup, buprenorphine-dependent subjects; C-TR, controls' threshold; M-TR, methadone-dependent subjects' threshold; B-TR, buprenorphine-dependent subjects' threshold; C-TL, controls tolerance; M-TL, methadone-dependent subjects' tolerance; B-TL, buprenorphine-dependent subjects' tolerance

Oral Opioid Administration and Hyperalgesia in Patients with Cancer or Chronic Non-malignant Pain

Igor Resnikov, Dorit Pud, Elon Eisenberg

British Journal of Clinical Pharmacology
2005; 60 (3):311-318

Design: Cross comparison of individuals with CNCP on non-opioid, weak and strong opioid analgesics

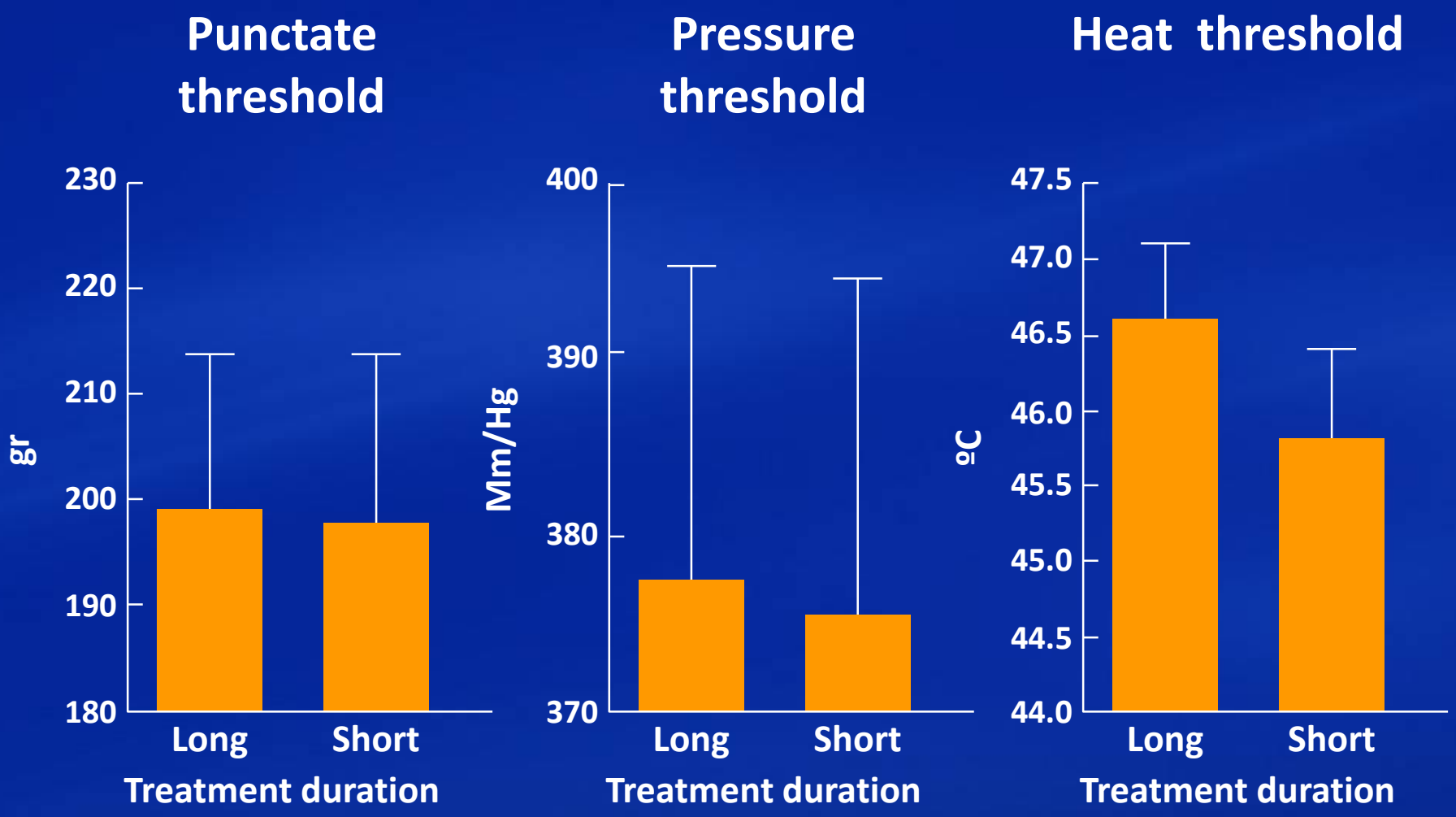
Participants: CNCP ≥3 months

Controls: CNCP without opioids

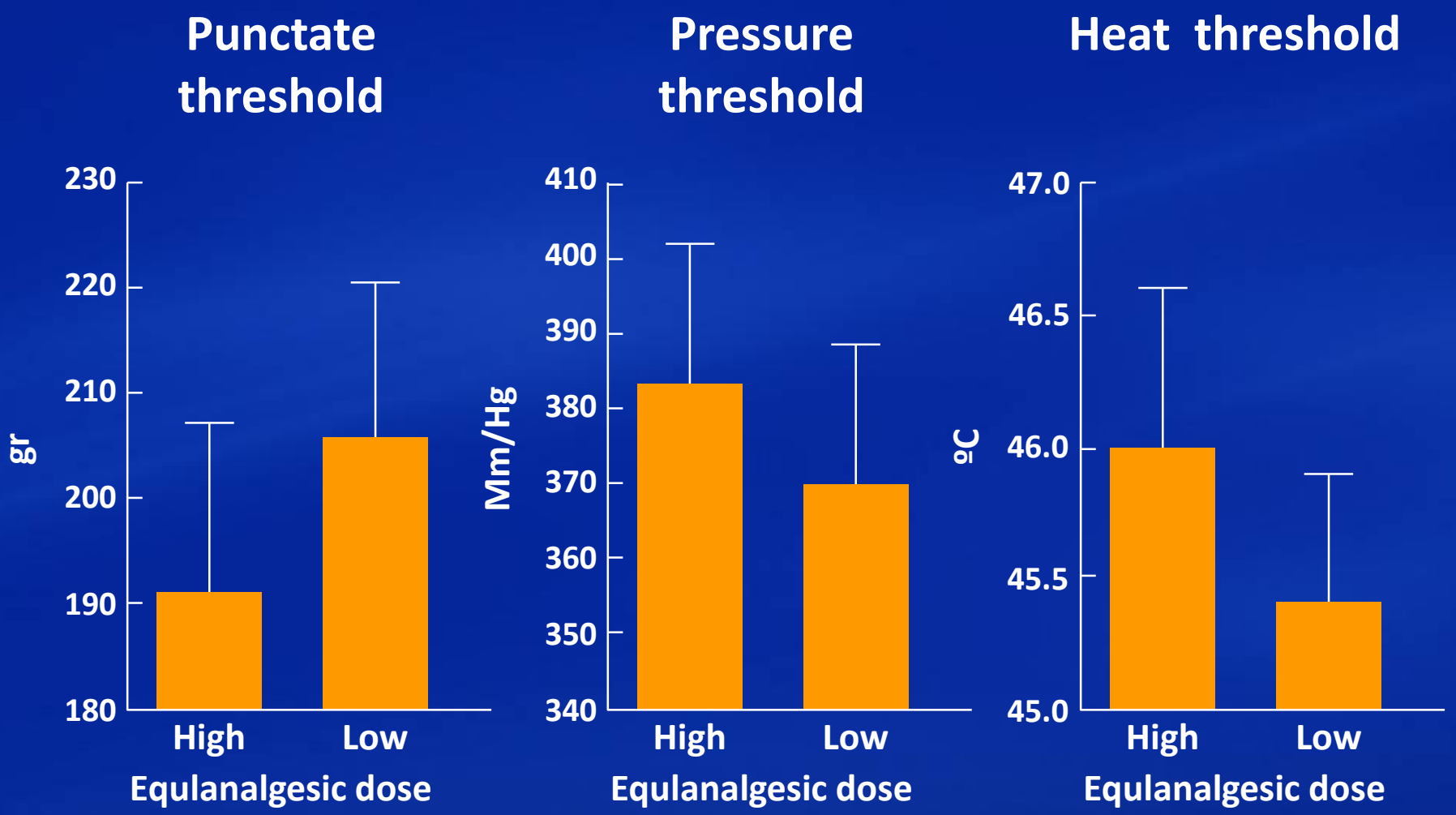
Intervention: Mechanical pain and threshold

Heat pain and threshold

Results: Short vs. Long Term



Results: High vs. Low Dose



Longitudinal Observation of Changes in Pain. Sensitivity During Opioid Tapering in Patients with Chronic Low-Back Pain

Hail Wang, Michael Akbar, Nina Weinsheimer, et al.

Pain Medicine

2011; 12:1720-1726

Design: 3 group comparison

- CLBP + opioid (1)
- CLBP – Opioid (withdrawal) (2)
- Healthy controls (3)

Participants: CLBP ± Opioids

Intervention: Cold pressor test

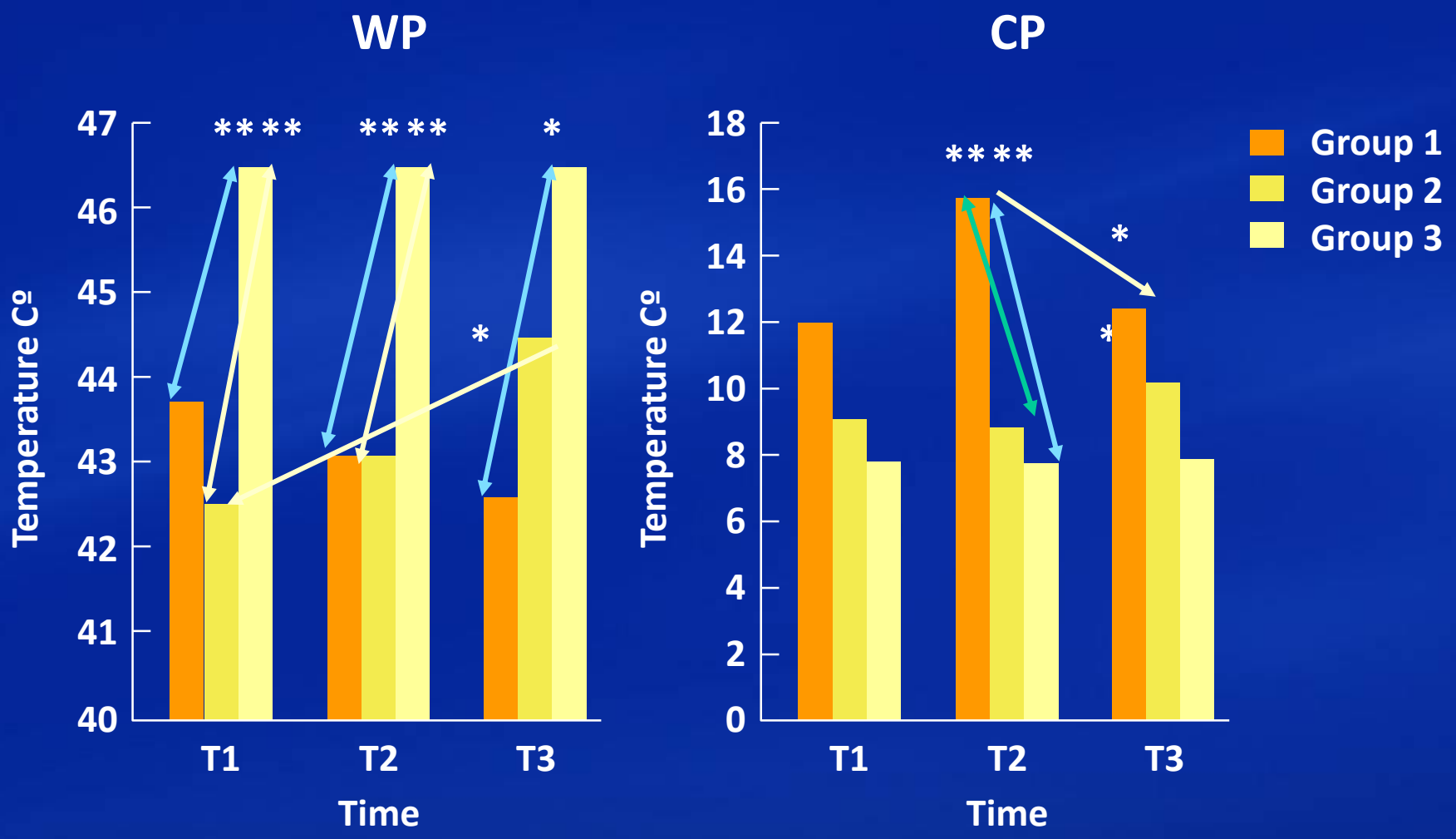
Heat test

Outcomes: Cold sensation, pain threshold

Heat pain threshold

3 time periods: day 0, 3 weeks, 6 months

Results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*
T1
T2
T3
Time
Group 1
Group 2
Group 3

Results

- Individuals stopped at perception of pain, but not tolerance to pain

Does Long-term opioid Therapy Reduce Pain Sensitivity of Patients with Chronic Low Back Pain? Evidence from Quantitative Sensory Testing

Hail Wang, Christian Fischer, Gang Chen, et al.

Pain Physician

2012; 15:ES135-ES143

Design: 3 group comparison

- CLBP + opioid (1)
- CLBP – Opioid (withdrawal) (2)
- Healthy controls (3)

Participants: CLBP ± Opioids

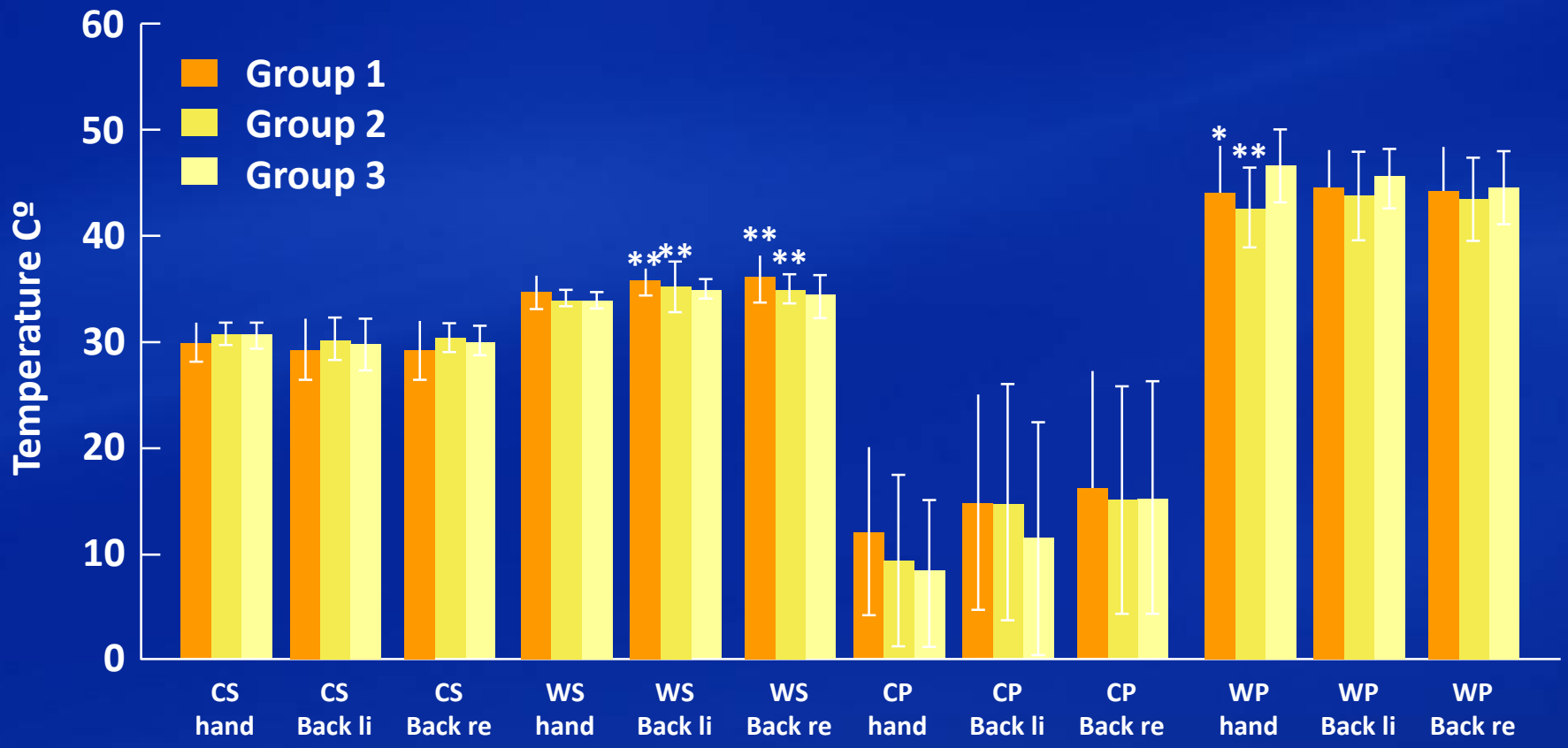
Controls: Healthy Individuals

Intervention: Cold detection thresholds and pain

Warm detection thresholds and pain

Outcomes: Perception and pain thresholds

Results


Temperature Cº
60
50
40
30
20
10
0
Group 1
Group 2
Group 3
*
**
**
**
**
**
CS hand
CS Back li
CS Back re
WS hand
WS Back li
WS Back re
CP hand
CP Back li
CP Back re
WP hand
WP Back li
WP Back re

Associations between Heat Pain Perception and Opioid Dose Among Patients with Chronic Pain Undergoing Opioid Tapering

William Hooten, Carlos Mantilla, Paola Sandroni

Pain Medicine

2010; 11:1587-1598

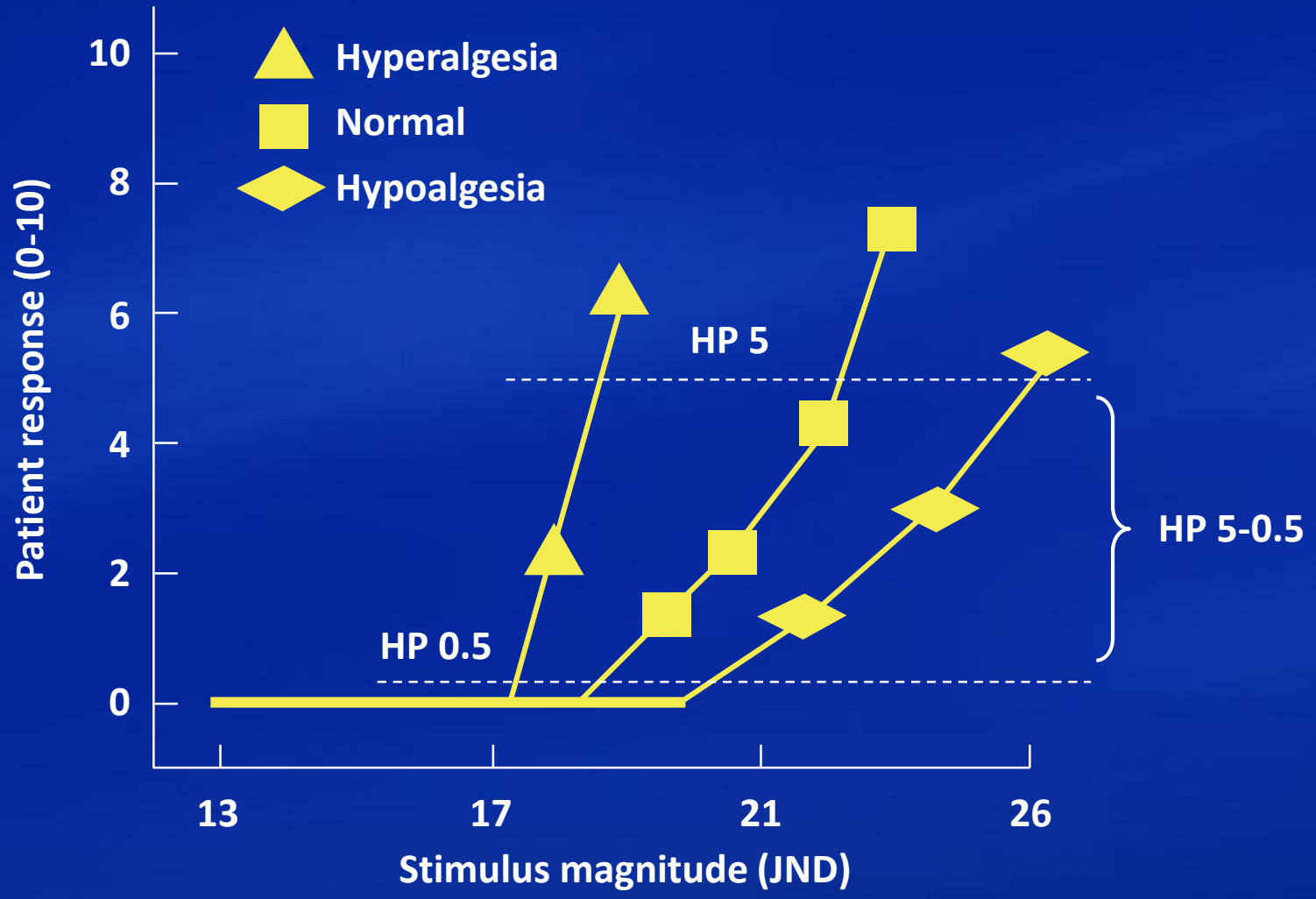
Design: Cross comparison of individuals with pain on and not on opioids

Patients: Heterogeneous patients population in pain

Controls: Pain patients not on opioids, tapered

Intervention: Heat perception Heat pain Heat perception to heat pain

Results


Hyperalgesia
Normal
Hypoalgesia
Patient response (0-10)
10
8
6
4
2
0
HP 5
HP 0.5
HP 5-0.5
13
17
21
26
Stimulus magnitude (JND)

Results

- Higher opioid doses greater hyperalgesia (lower HP5-0.5)
- Taper lead to hypoalgesia (higher HP5-0.5)
  - Right-shifted curve

Conditioned Pain Modulation (DNIC)

Increased Pain Sensitivity in chronic Pain Subjects on Opioid Therapy: A Cross-Sectional Study using Quantitative Sensory

Y. Zhang, Shihab Ahmed, Trang

Pain Medicine

2014; in press

Design: 3 group comparison

- CLBP + opioid (1)
- CLBP – Opioid (withdrawal) (2)
- Healthy controls (3)

Patients: Opioid tolerant chronic pain patients

Controls: Chronic pain and no opioids

Healthy Individuals

Intervention: Cold and warm thresholds

Cold and warm pain thresholds

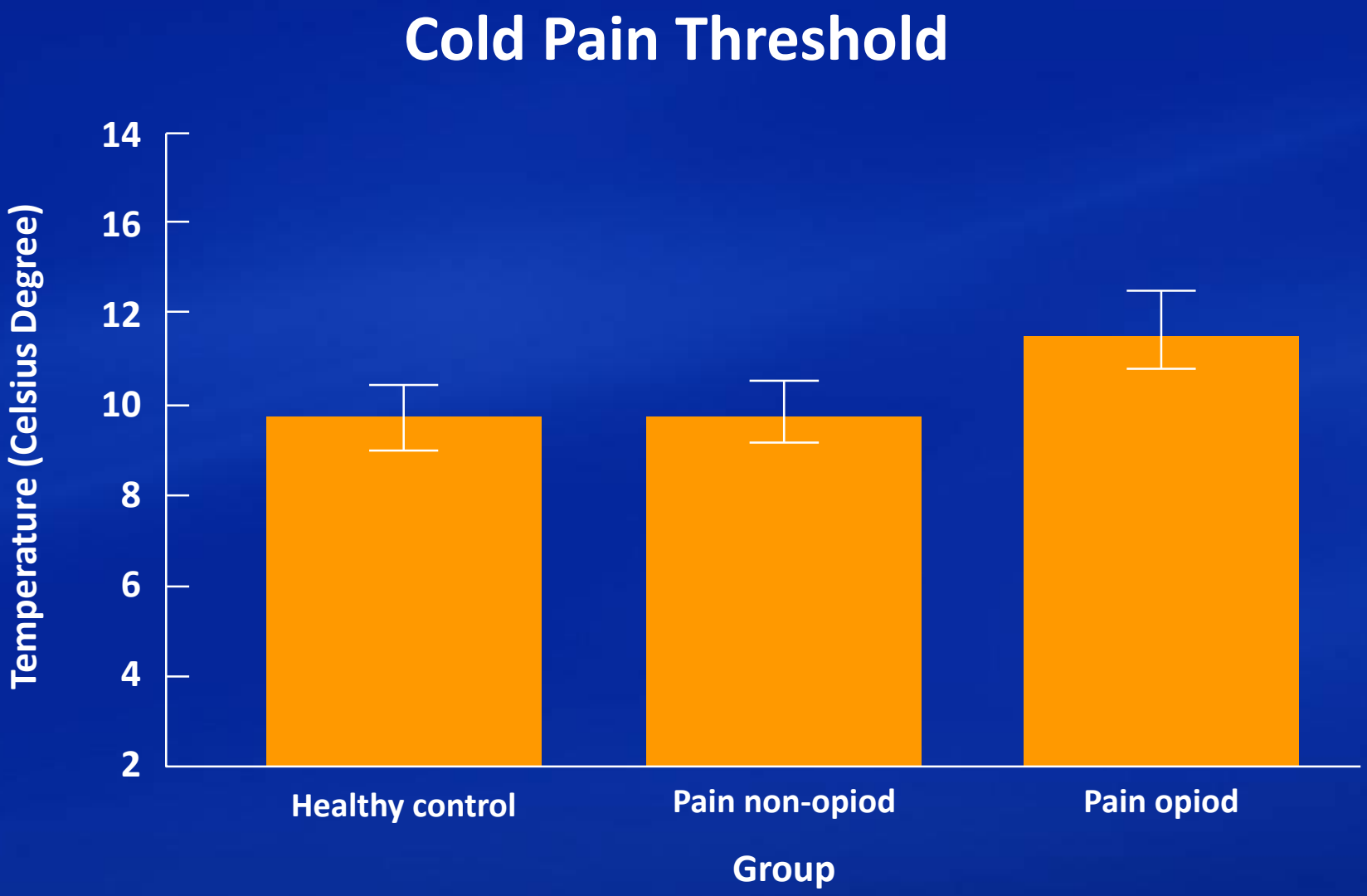
Cold and warm pain tolerance

Temporal summation

Conditioned pain modulation

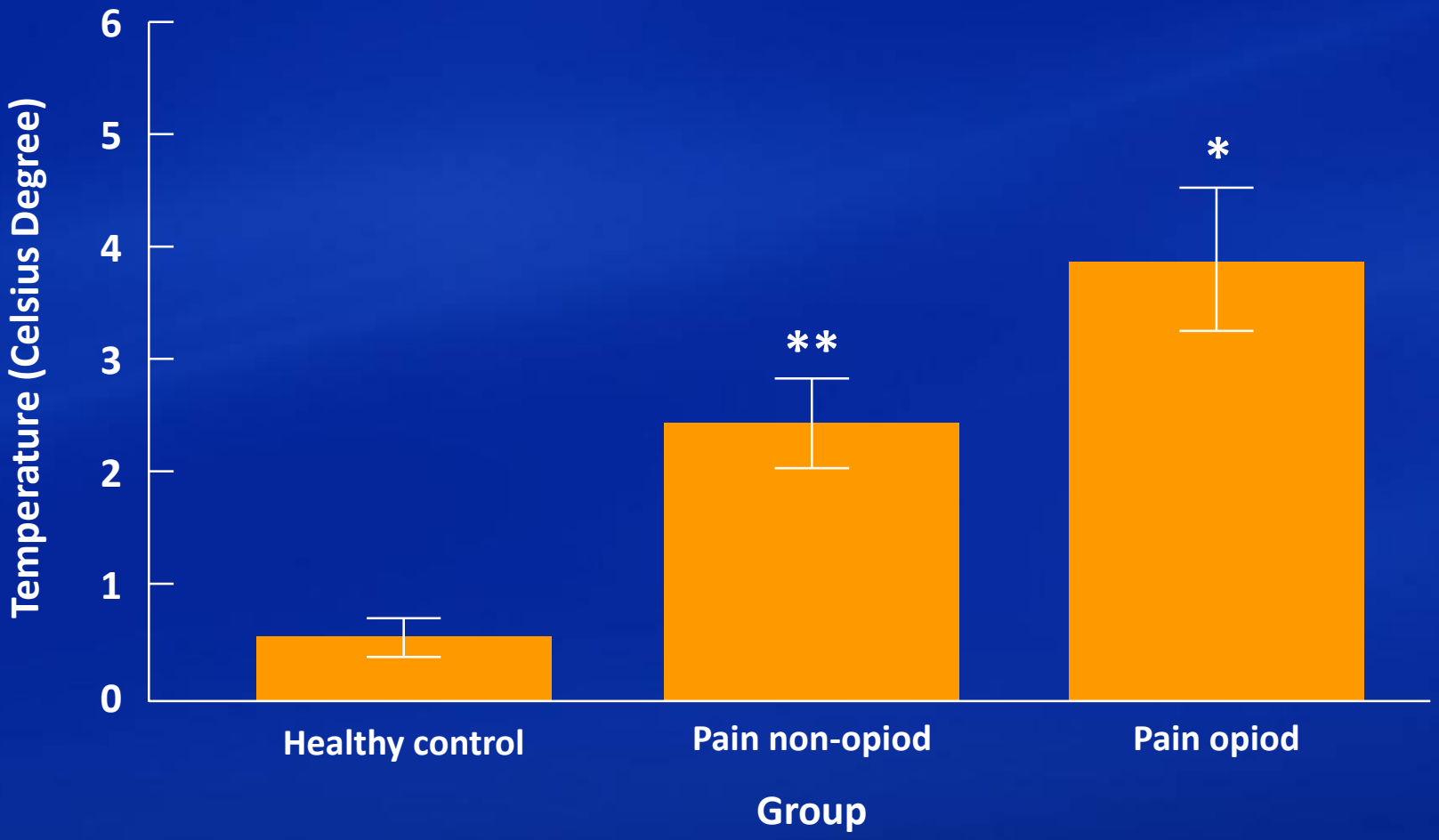
Outcomes: Same as above

Results


Cold Pain Threshold
Temperature (Celsius Degree)
14
16
12
10
8
6
4
2
Healthy control
Pain non-opiod
Pain opiod
Group

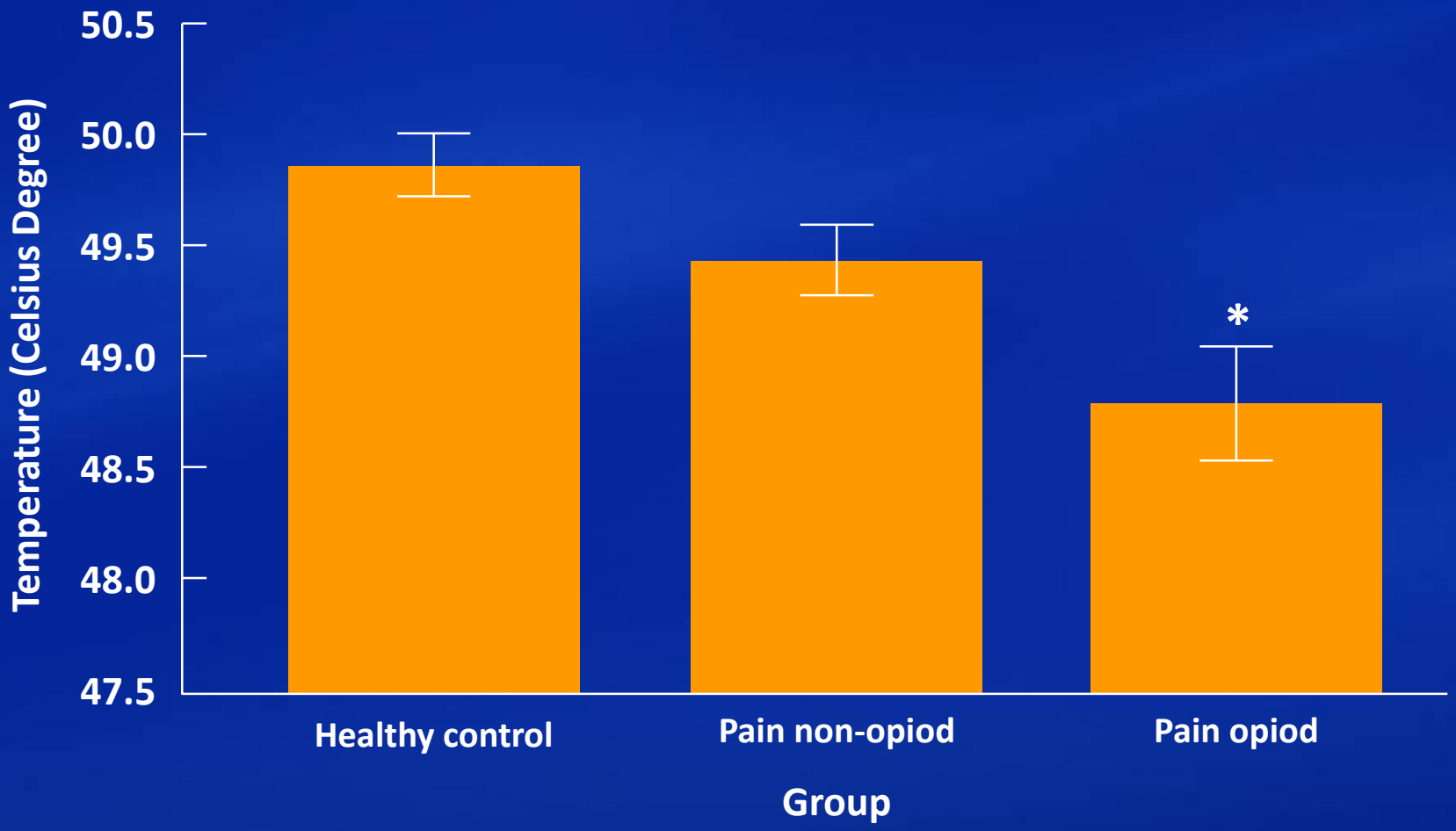
Results

Lowest Tolerated Cold Pain Temperature



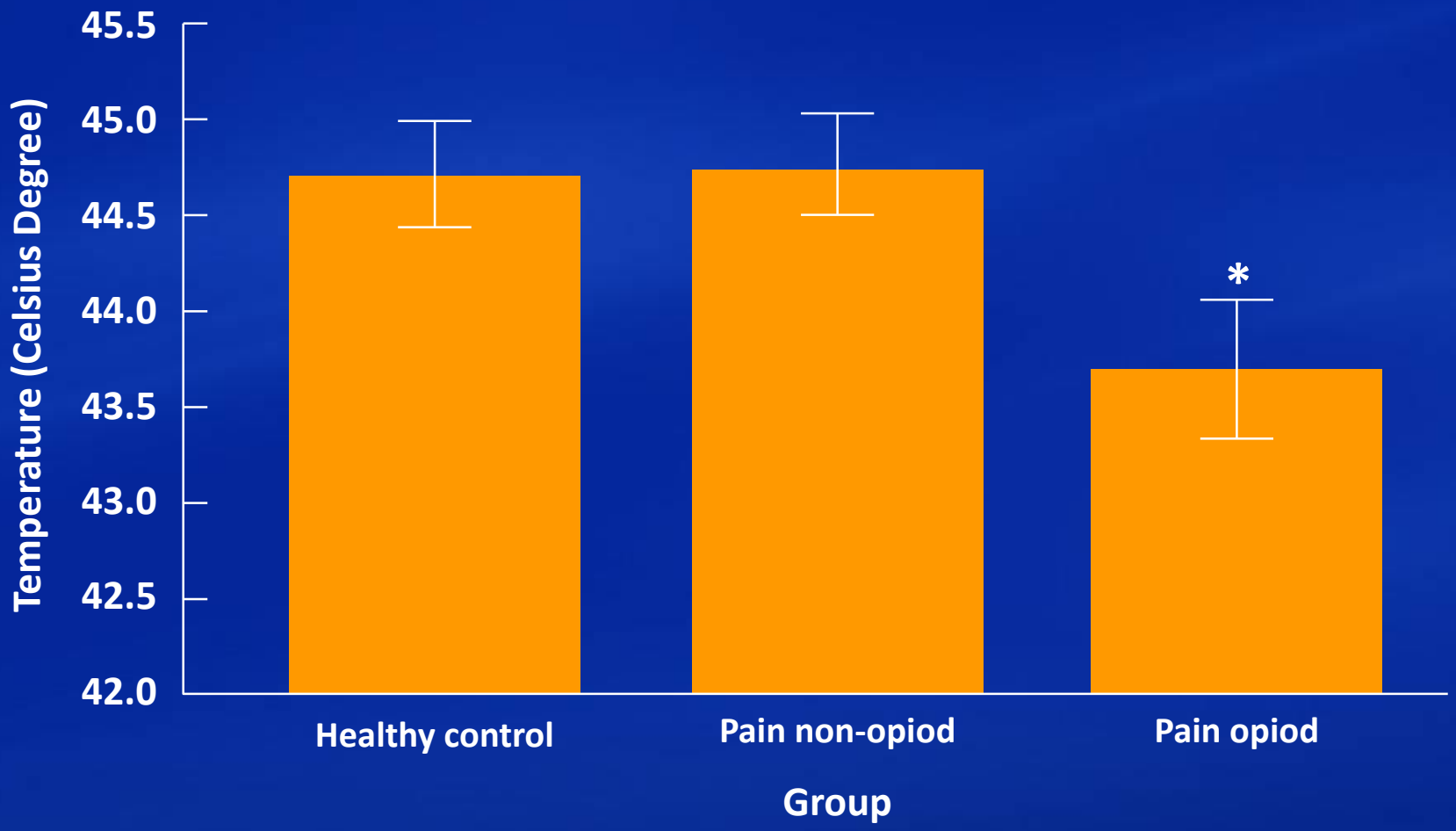
Results

Maximal Tolerated Temperature



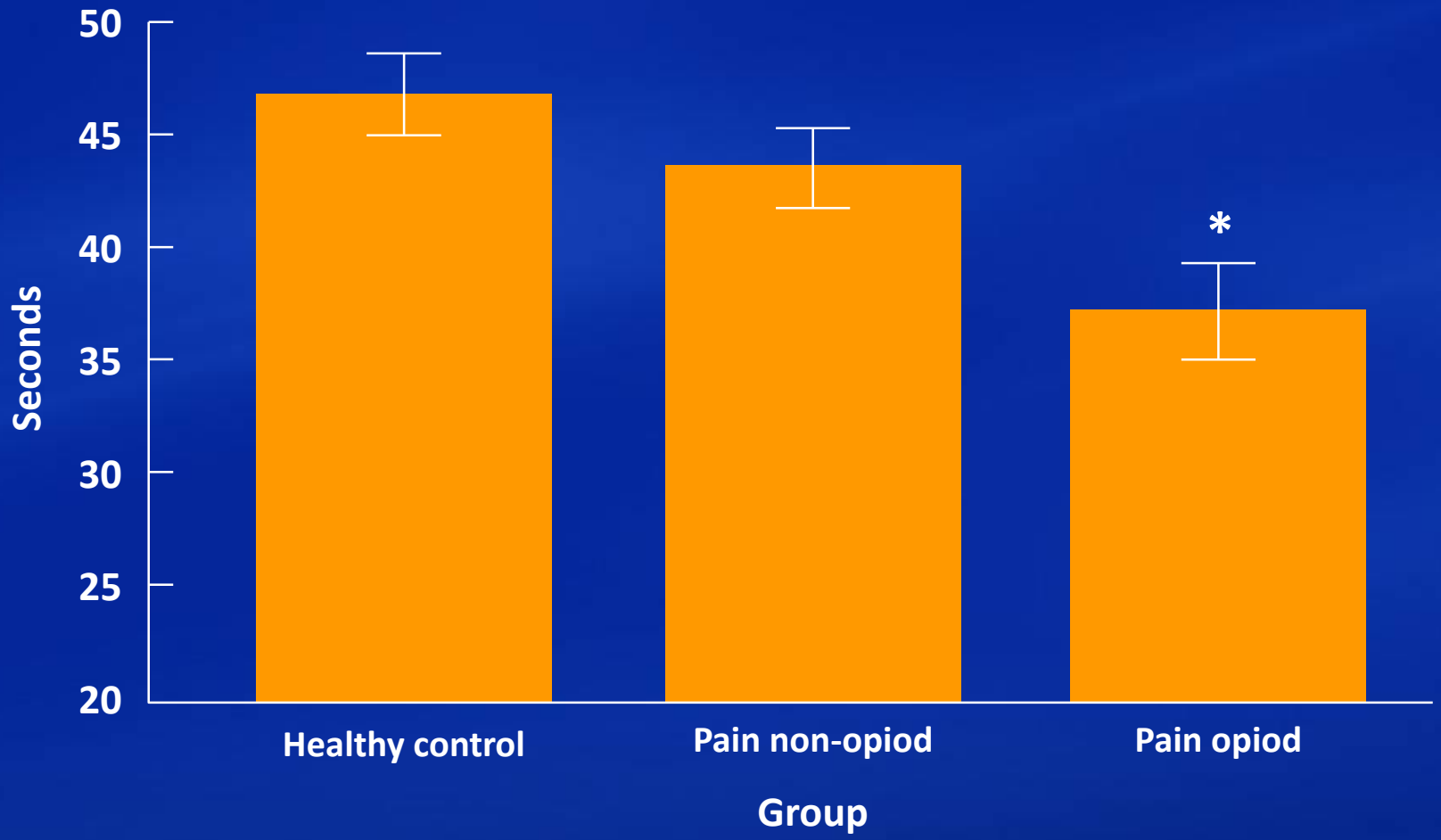
Results

Heat Pain Threshold



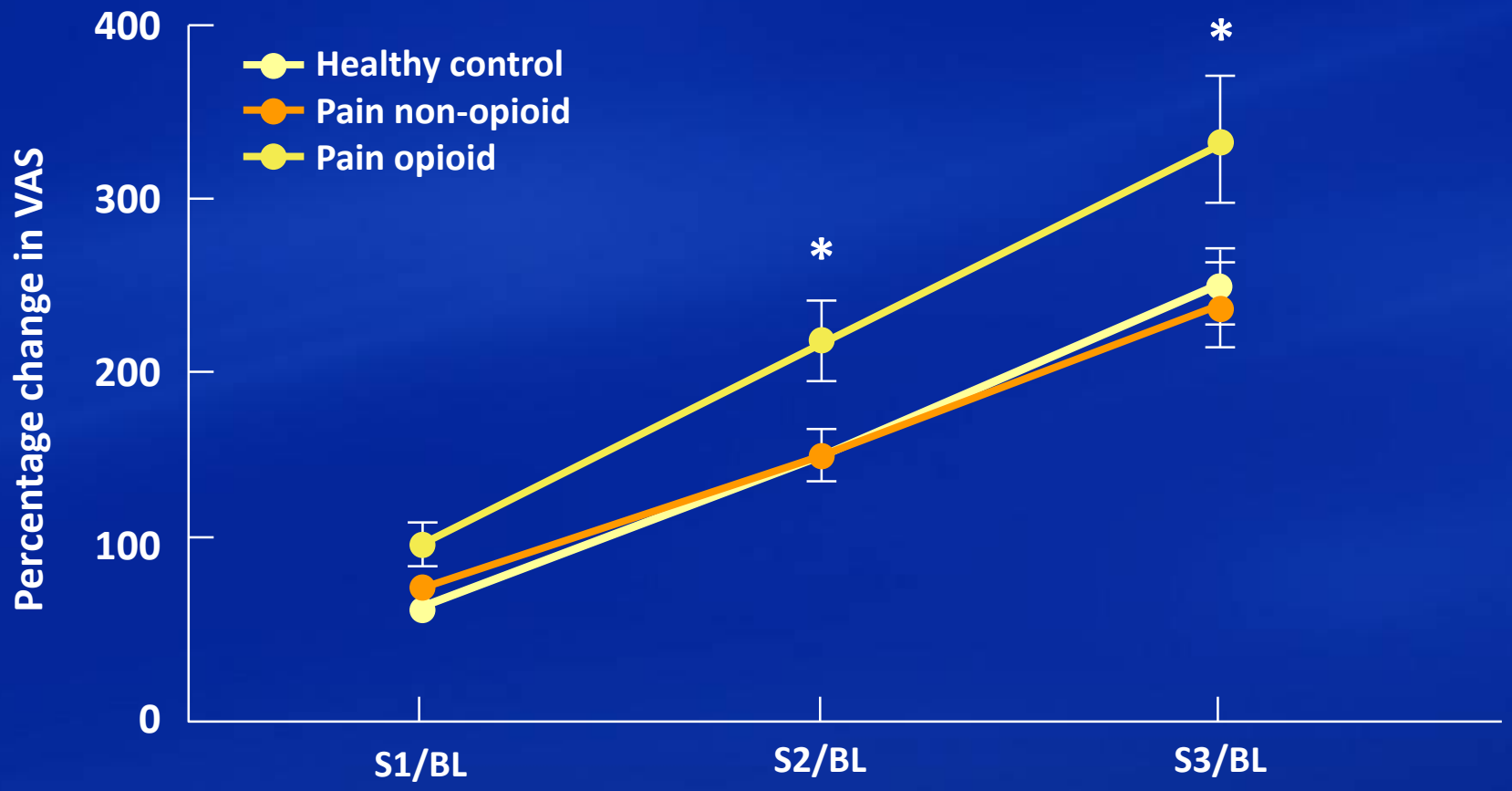
Results

Supra-threshold Heat Pain Tolerance



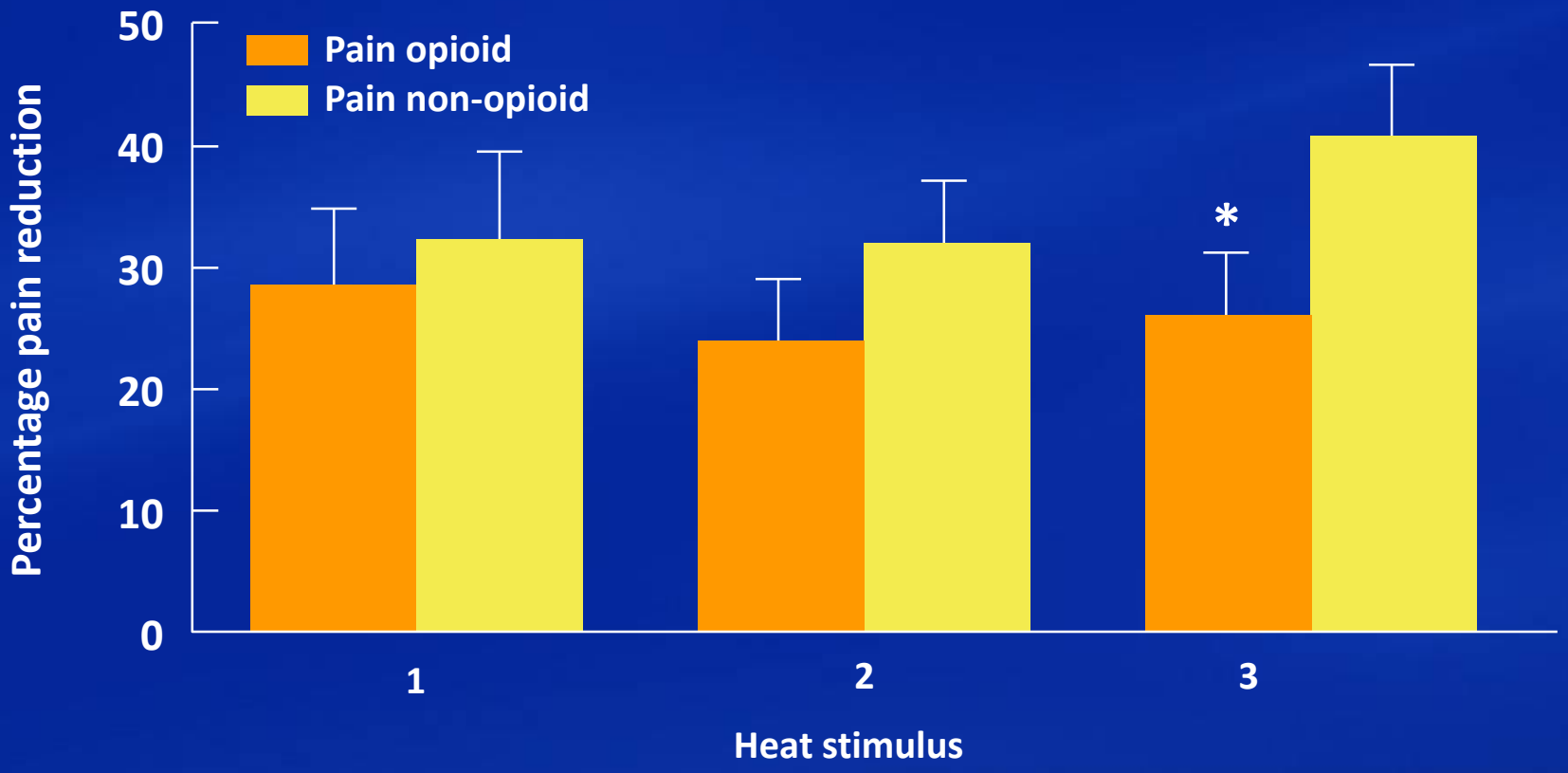
Results

Pain Summation



Results

Magnitude of DNIC



Diffuse noxious inhibitory control (DNIC) in chronic pain subjects on opioid and non-opioid therapy.

*P ≤0.05 pain opioid group compared with pain non-opioid group.

Oral Opioid Use Alters DNIC but not Cold Pain Perception in Patients with Chronic Pain – New Perspective of Opioid-Induced Hyperalgesia

Krestin Ram, Elon Enenberg, May Haddad, et al.

Pain
2009;139:431-438

Design: Comparison of chronic pain patients (cancer and non-cancer) on opioid and not on opioids

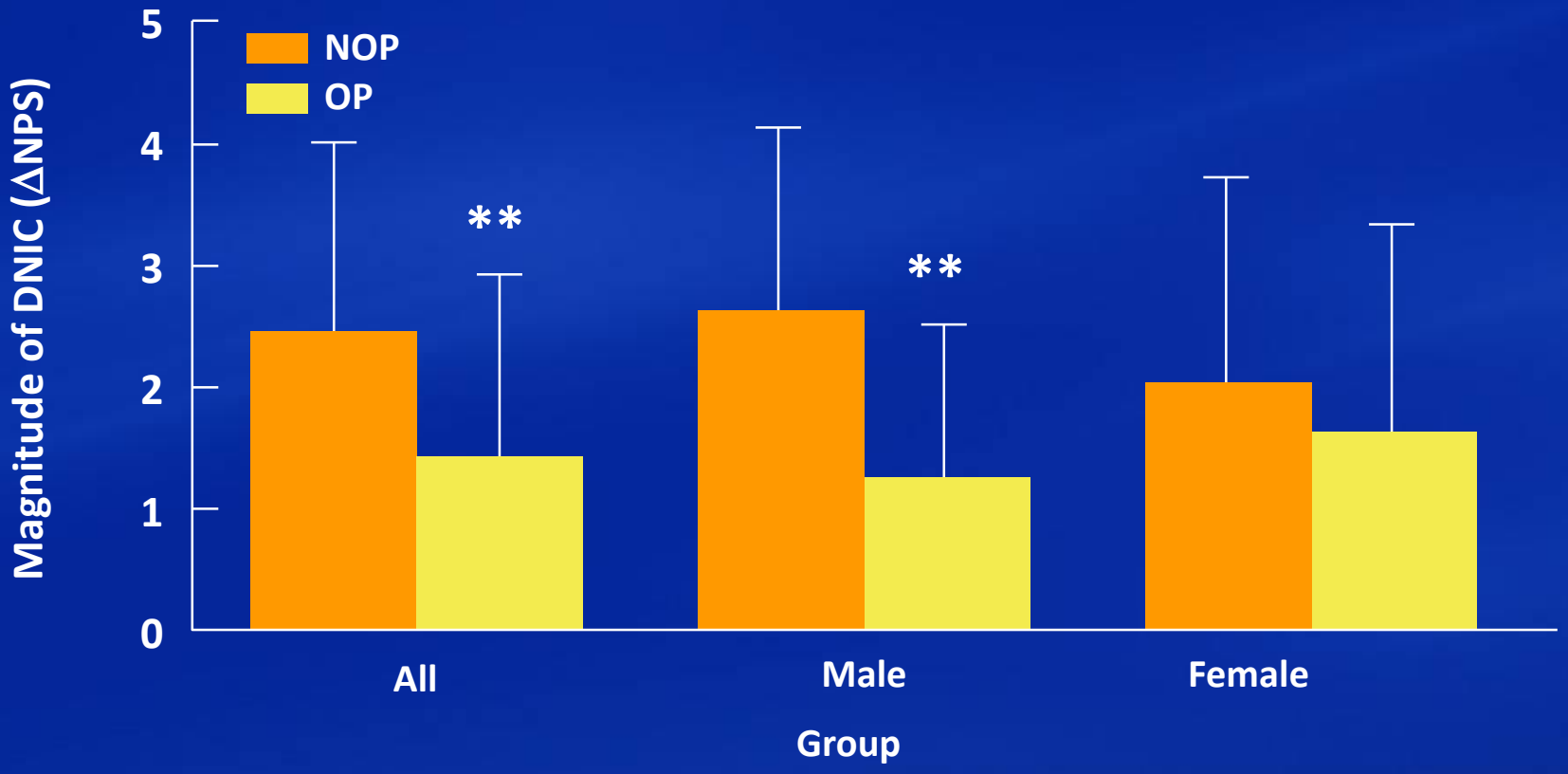
Patients: As above

Controls: Chronic cancer patients not on opioids

Intervention: Conditioned pain modulation Cold pressor test

Outcomes: DNIC Cold tolerance and pain

Results



Temporal Summation

Altered Quantitative Sensory Testing Outcome in Subjects with Opioid Therapy

Lucy Chen, Charlene Malarick, Lindsey Seefeld

Pain
2009;143:65-70

Design: 3 group comparison

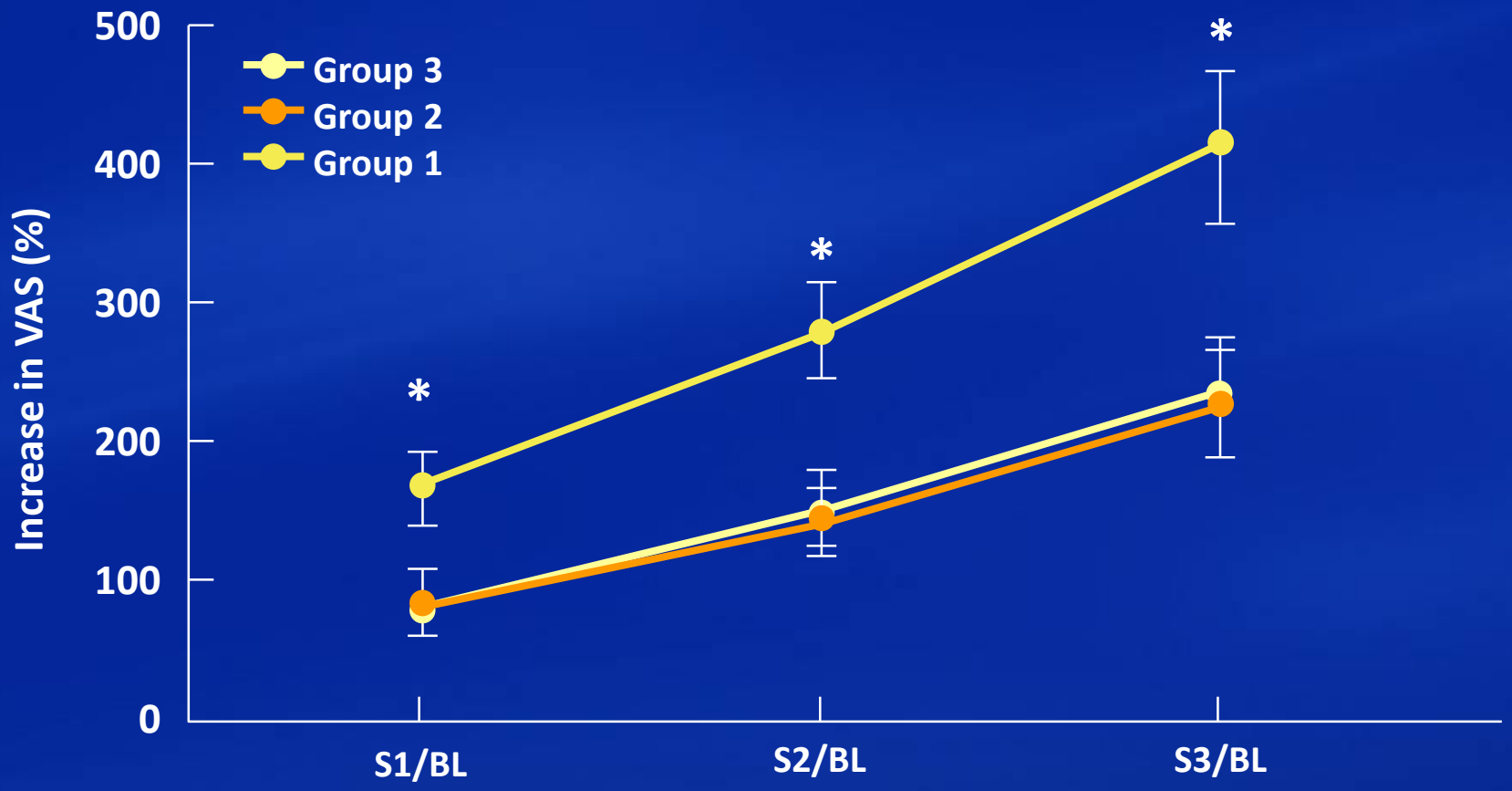
- CLBP + opioid (1)
- CLBP – Opioid (withdrawal) (2)
- Healthy controls (3)

Patients: CNCP on opioids

Controls: Health controls, CNCP not on opioids Intervention: Cold and heat thresholds Cold and heat pain thresholds Cold and heat tolerance Temporal summation to heat stimulus Mechanical pain thresholds

Outcomes: Differences between thresholds, pain and tolerance between groups Correlation with opioid doses

Results


500
400
300
200
100
0
Increase in VAS (%)
Group 3
Group 2
Group 1
*
*
*
S1/BL
S2/BL
S3/BL

Results

- Heat pain sensitivity was the result of pain and not opioid
- Increased temporal summation was the result of the opioid

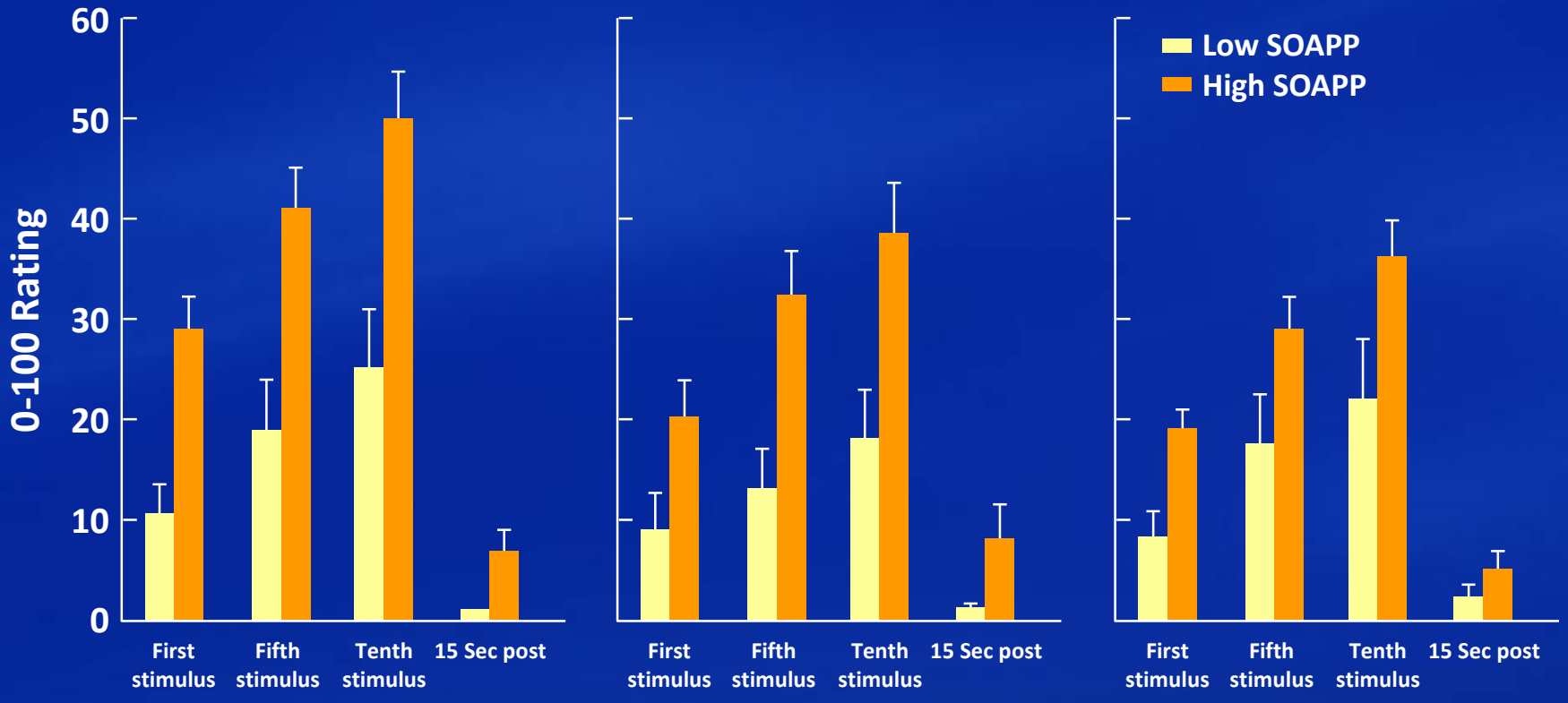
Elevated Pain Sensitivity in Chronic Pain Patients at Risk for Opioid Misuse

Robert Edwards, Ajaj Wasan, Ed Michna, et al.

Journal of Pain
2011;12(9):953-963

Design:	Cross-sectional cohort study
Patients:	Individuals with spinal pain (CNCP)
Controls:	Cross comparison using opioid doses
Intervention: temporal	SOAPP-R abuse risk Catastrophizing summation pressure pain thresholds Heat and cold thresholds Heat and cold pain thresholds

Results: A- No Opioid to C-High Opioid Dose



Results

- Mechanical pain correlated with SOAPP-R
- Pain threshold inversely correlated with SOAPP-R
- No association with opioid doses

Local Anesthetic Injection Pain and Unpleasantness

The Effect of Opioid Dose and Treatment Duration on the Perception of a Painful Standardized Clinical Stimulus

Steven Cohen, Paul Christo, Shuxing Wang

Regional Anesthesia and Pain Medicine
2008;33(3):199-206

Design: 2 group comparison

- Healthy controls
- Individuals undergoing interventional procedure

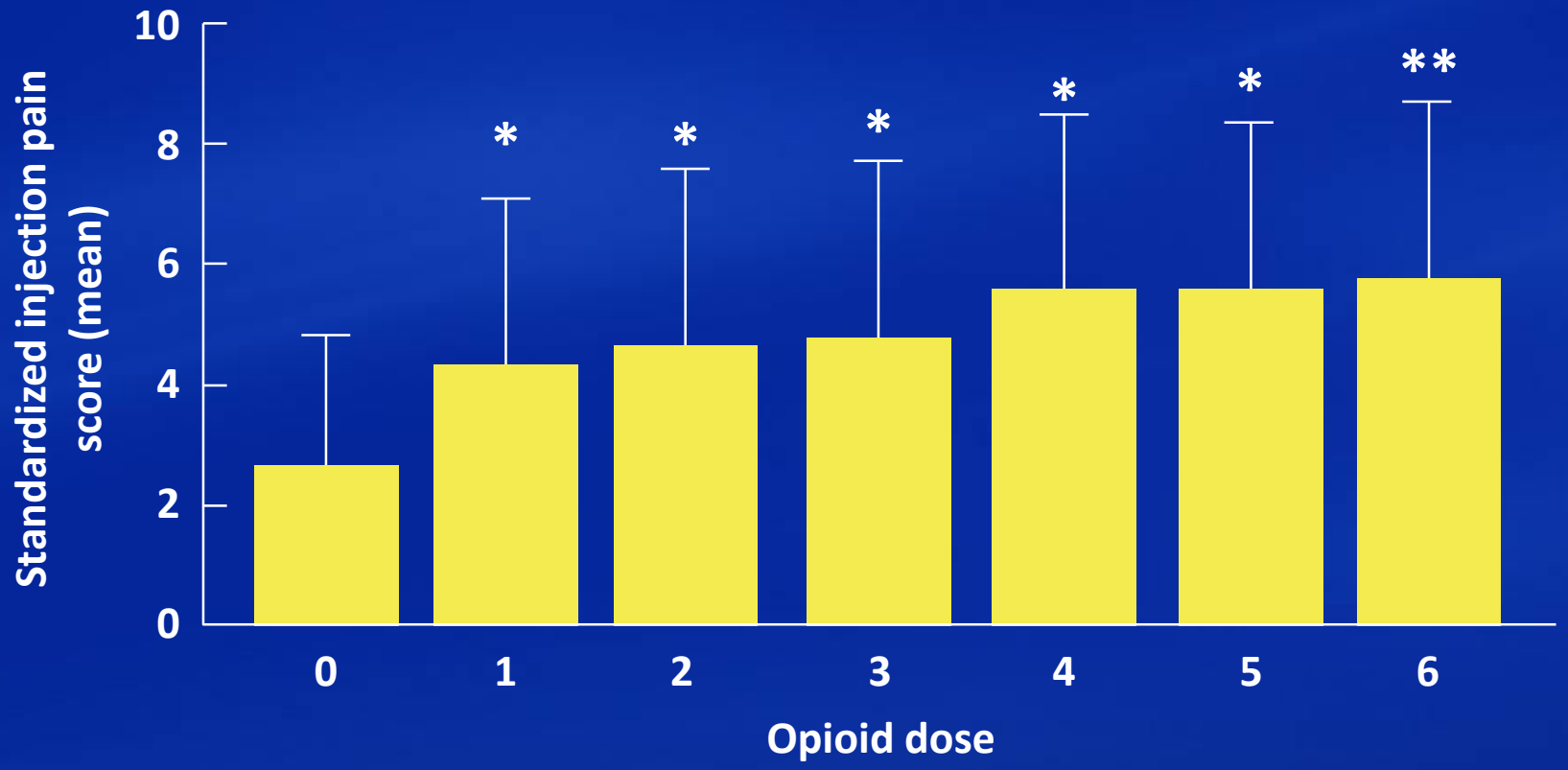
Patients: Individuals undergoing interventional procedures on opioids

Controls: Volunteers

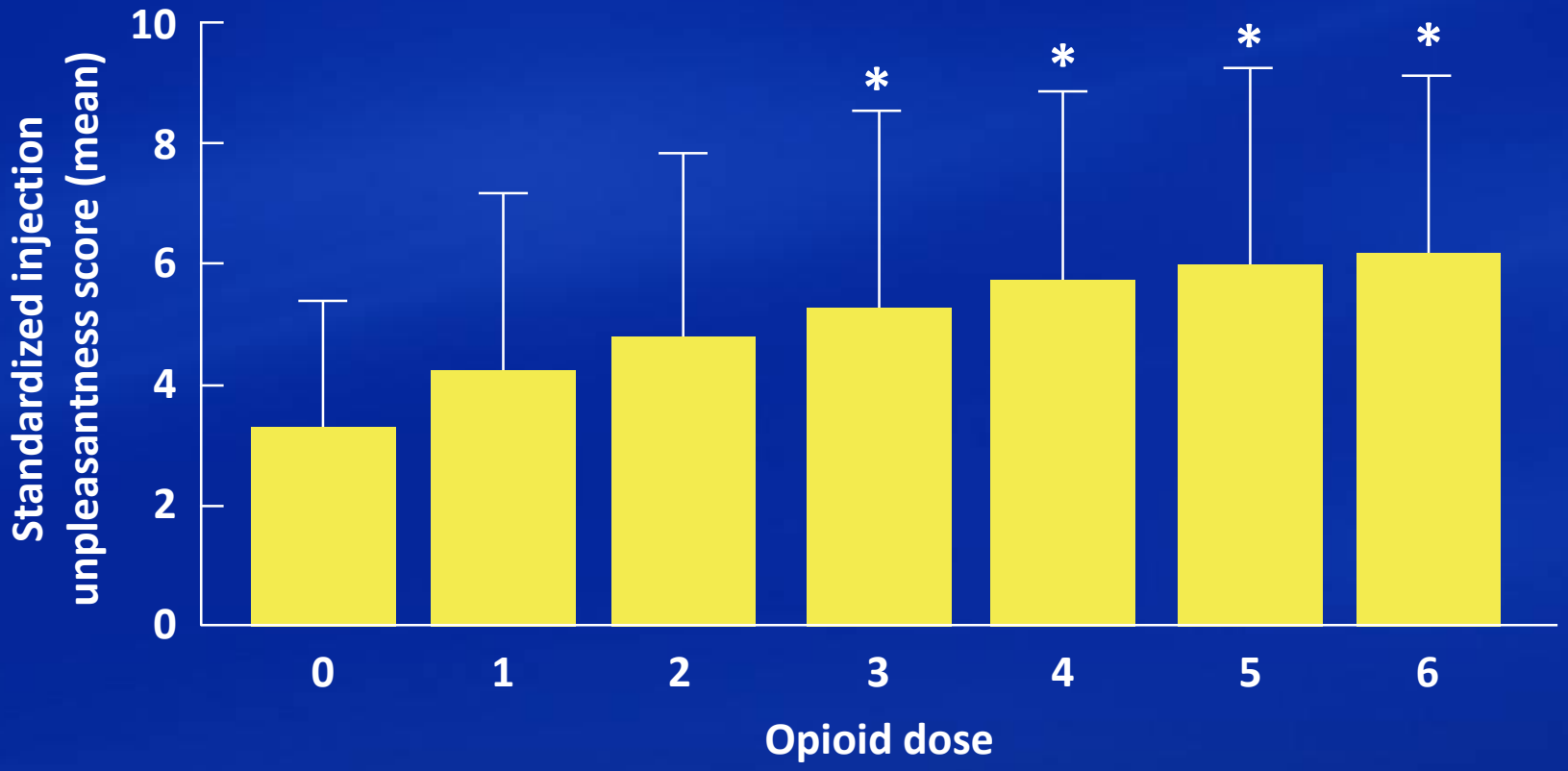
Intervention: Local anesthetic injection

Outcomes: Pre-anesthetic opioid dose
Pain from injection
Unpleasantness from injection

Results: 0 - No Opioid to 6 - >300mg MED



Results: 0 - No Opioid to 6 - >300mg MED



High-Dose Daily Opioid Administration and Poor Functional Status Intensify Local Anesthetic injection Pain in Cancer Pain

Shin Kim, Duck Yoon, Kwan Choi, et al.

Pain Physician
2013;16:E247-E256

Design: 2 group comparison

- Cancer patients not on opioids
- Cancer patients on opioids

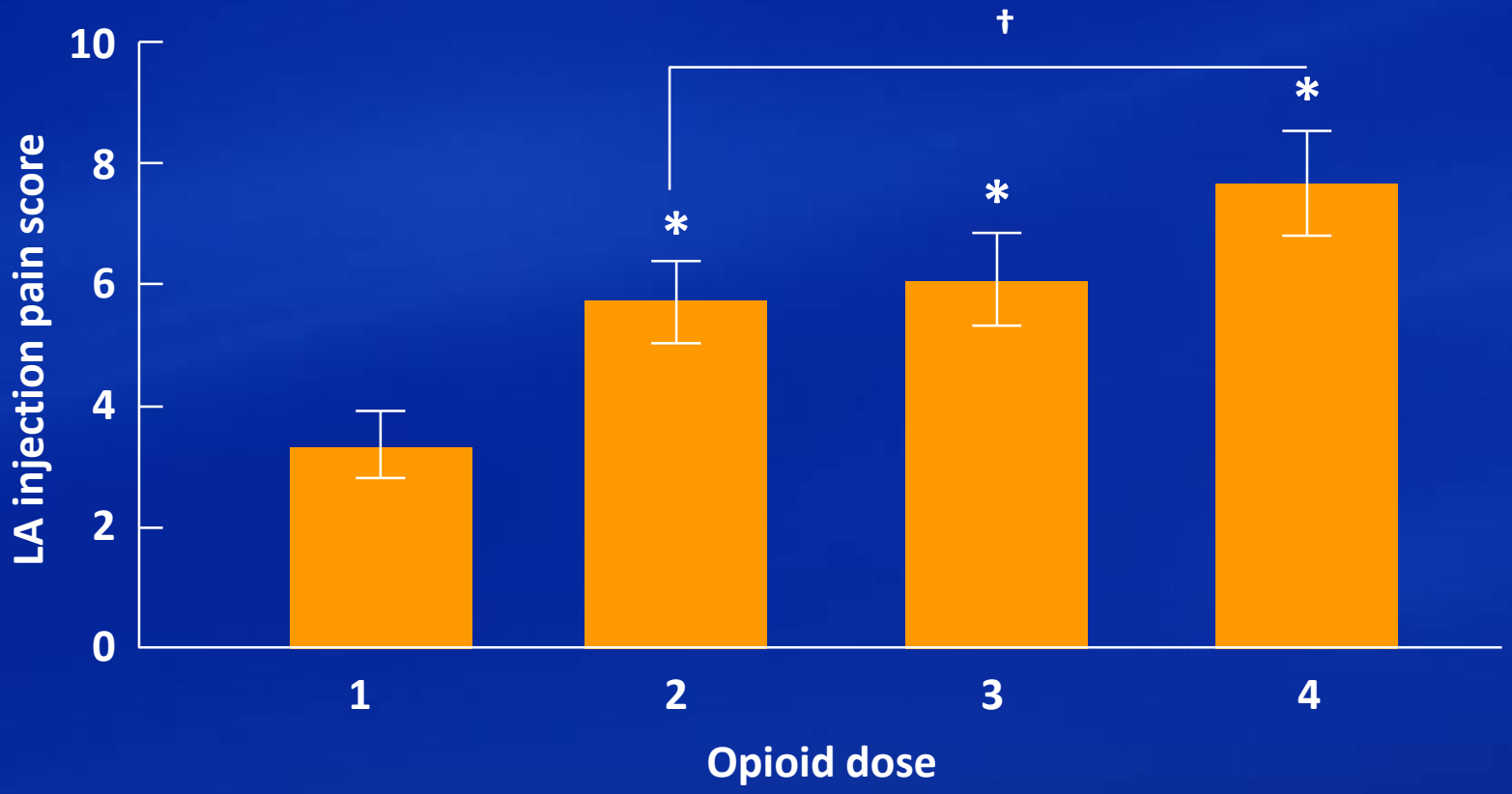
Patients: Cancer patients on opioids

Controls: Cancer patients not on opioids

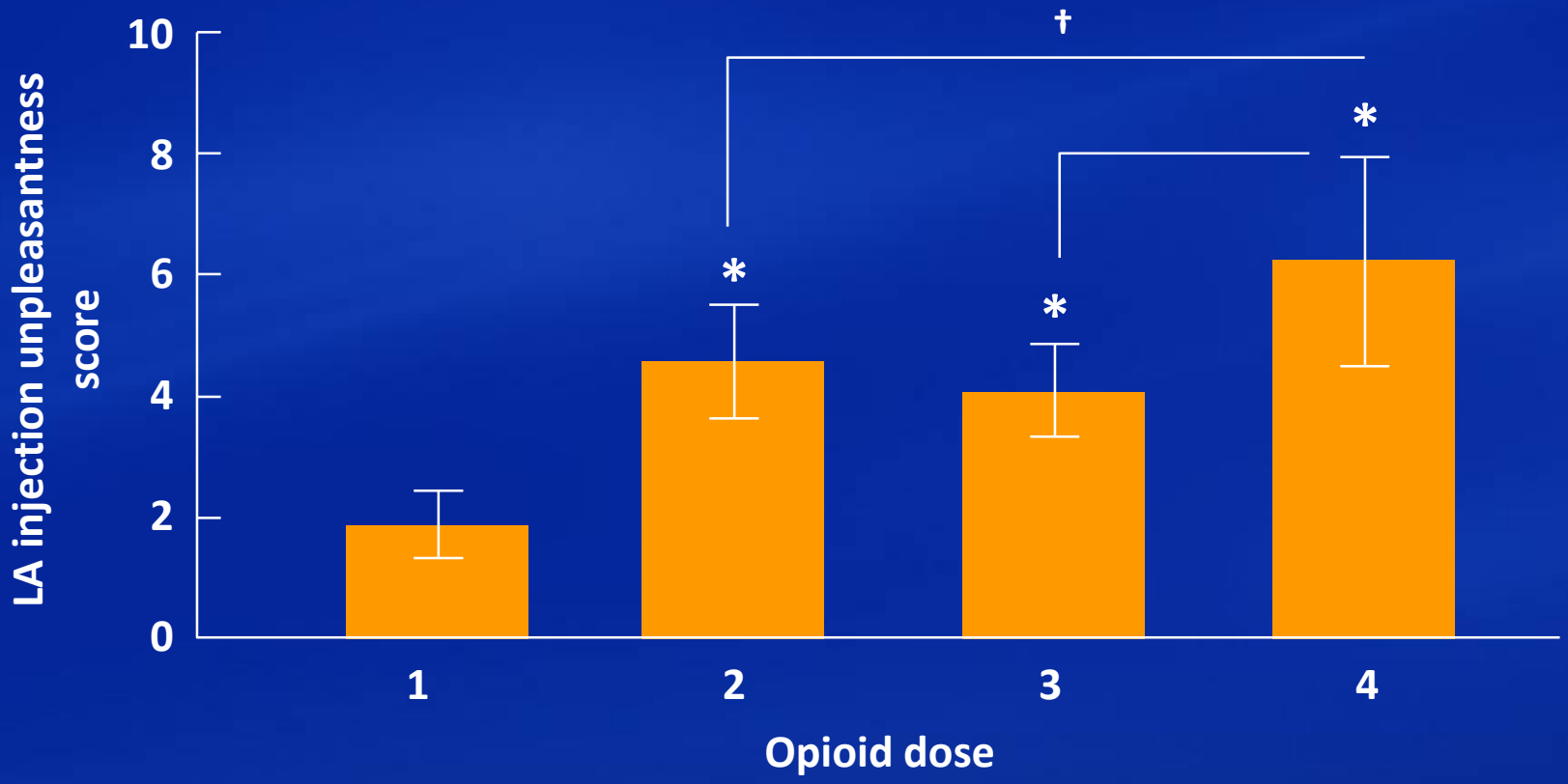
Intervention: Diagnostic or therapeutic nerve block, local anesthetic

Outcomes: BPI Pain and unpleasantness to injection, behavior pain

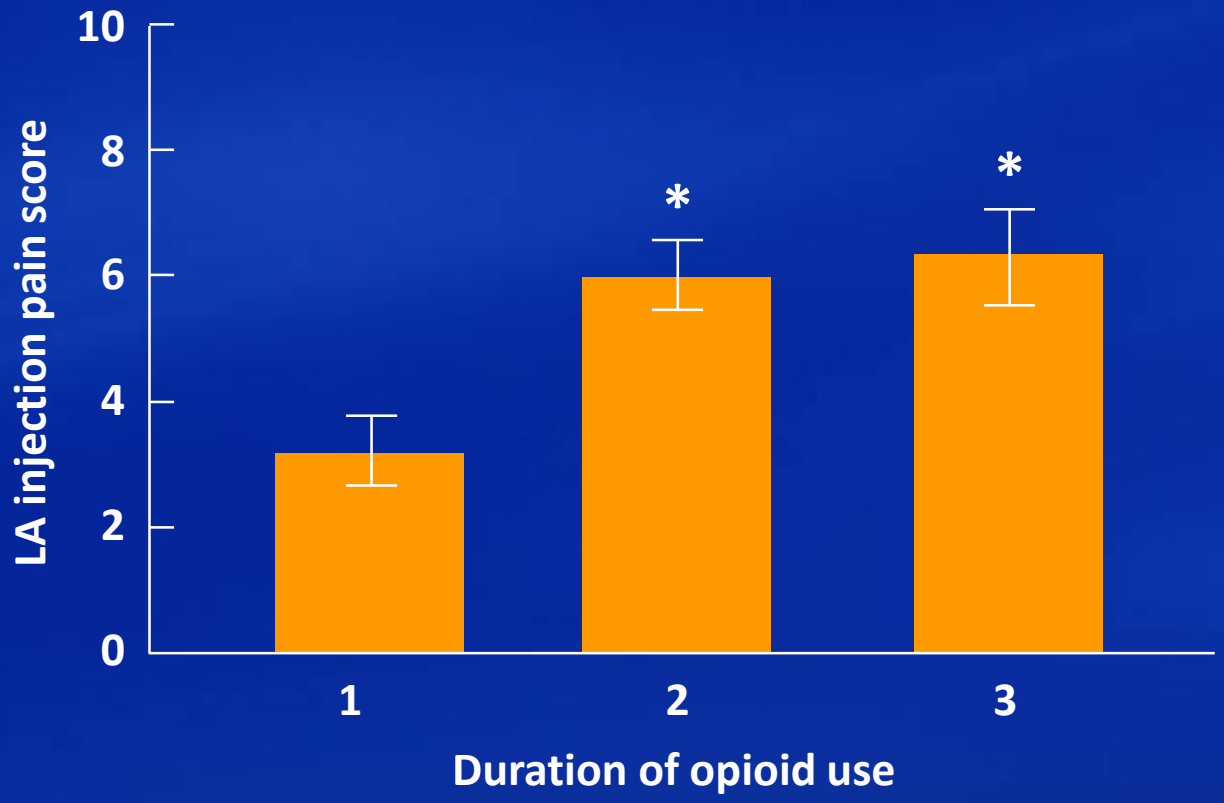
Results: 1 - No Opioid to 4 – > 200MED



Results: 1 - No Opioid to 4 - > 200MED



Results: 1 - No Opioid to 3 - > 1 Year



Post-Surgery Hyperalgesia

Opioid-Induced Hyperalgesia in Patients after Surgery: A Systematic Review and a Meta-analysis

D. Fletcher, V. Martinez

British Journal of Anesthesia
2014;112(6):991-1004

Design: Meta-analysis

Patients: Individuals undergoing surgery who received intra-operative remifentanil fentanyl, sufentanil

Controls: Individuals undergoing surgery who received none of the opioids or low doses

Intervention: Surgery, intra-operative opioid administration

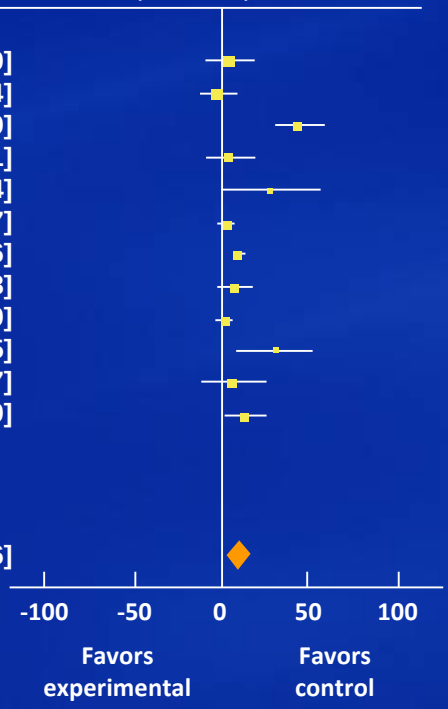
Outcomes: Pain at rest 24 hours after surgery Cumulative morphine equivalents over 24 hours Pain at 1 and 4 hours post-op Mechanical allodynia around the wound Opioid adverse events

Results

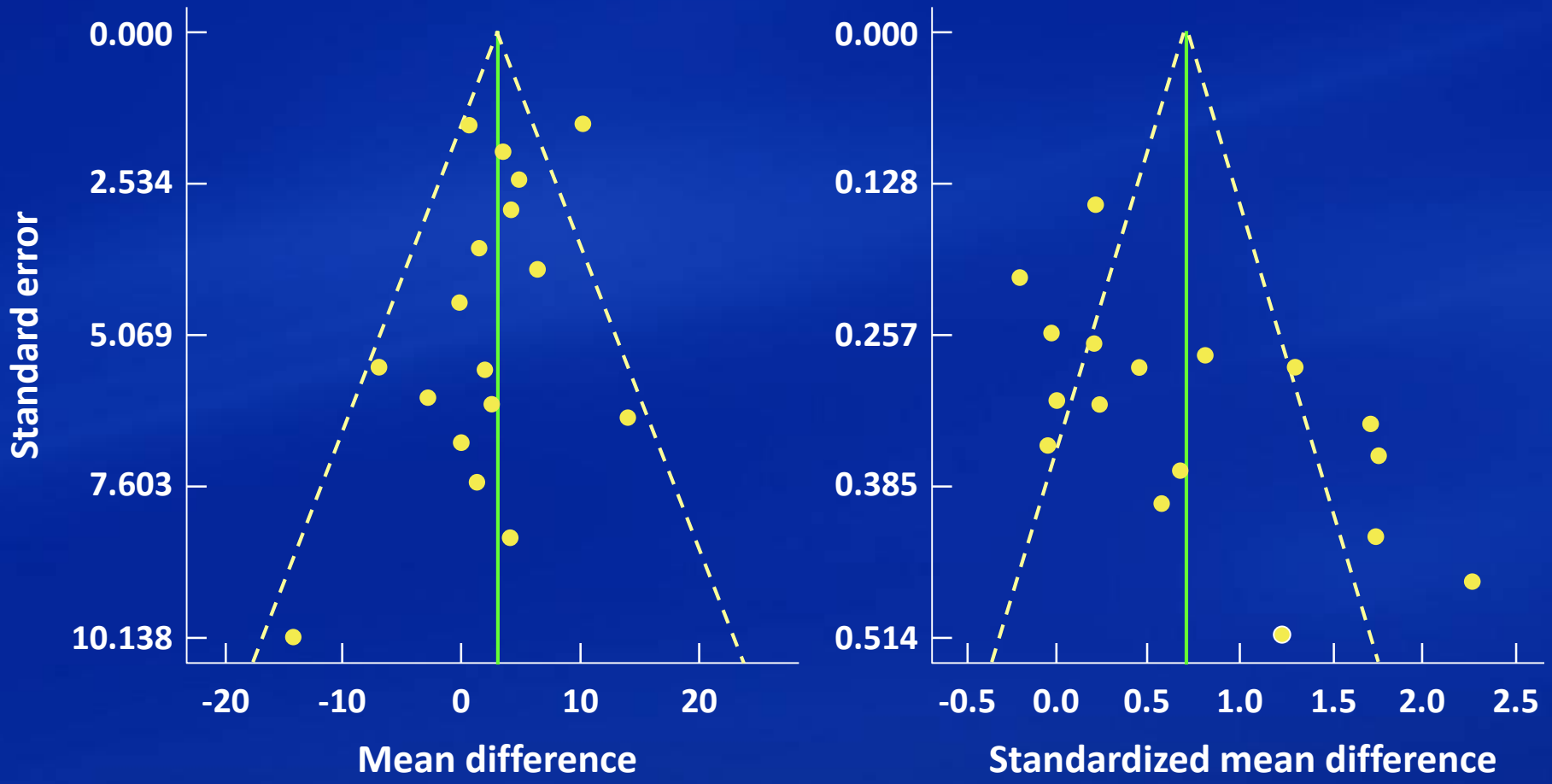
Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Pain at 1h								
Agata 2010	51.5	14.7	15	47.5	20.8	15	7.3%	4.00 {-8.89, 16.89]
Carvalho 2012	7.9	10	9	10.8	10	9	9.5%	-2.90 [-12.14, 5024]
Cho 2008	63.5	18	20	20	24.7	20	7.0%	43.50 [30.11, 56.89]
Cortinez2001	54	30	30	50	22	30	7.1%	4.00 [-9.31, 17.31]
Guignard 2001	67.7	18.9	24	39.9	57.8	20	2.9%	27.80 [1.36, 54.24]
Lee 2013	22.8	7.5	29	19.6	7.4	28	12.9%	3.20 [-0.67, 7.07]
Lee 2013a	51.4	4.2	29	41.4	6.2	40	13.5%	10.00 [7.54, 12.46]
Ryu 2007	45.7	22	30	38.5	11.5	30	9.7%	7.20 [-1.68, 16.08]
Shin 2010	37	16	88	35.1	10	98	12.9%	1.90 [-1.99, 5.79]
Terao 2010	70	31	13	40	25	13	3.9%	30.00 [8.35, 51.65]
Xuerong 2008	23	29	15	17	18	15	5.3%	6.00 [-11.27, 23.27]
Yeom 2012	70	18	20	57	20	20	7.9%	13.00 [1.21, 24.79]
Total (95% CI)			322			338	100.0 %	9.40 [4.35, 14.46]

Heterogeneity: t^2=47.80; x^2=57.06, df=11 (P<0.00001): I^2-81%

Test for overall effect: Z=3.64 (P=0.0003)



Results


Standard error
0.000
2.534
5.069
7.603
10.138
-20
-10
0
10
20
Mean difference
0.000
0.128
0.257
0.385
0.514
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
Standardized mean difference

Results

- Morphine equivalent dose consumption over 24 hours directly correlated with intra-operative administration of remifentanil, fentanyl, sufentanil

Summary

1. Is OIH modality specific?
   - OIH appears to be relatively modality specific, most often observed with reduced cold tolerance, temporal summation and conditioned pain modulation

Summary

2. Is OIH opioid specific and duration related?
   - OIH does not appear to be limited to a single opioid. OIH may be dose related, little is known about duration though OIH can be seen with single opioid doses.

Summary

3. Is there an association between OIH and opioid analgesic tolerance?
   - There are very few studies to answer this question. A single study of remifentinal analgesia in opioid tolerance individuals suggests that analgesic tolerance can occur without OIH.

     FIGURE 30

Summary

4. Is OIH a laboratory finding or does it have clinical relevance?
   - OIH increases pain sensitivity to local procedures, increases opioid requirements post-operatively. There is some suggestion that pain sensitivity independent of opioids predisposes to opioid abuse

Summary

5. Does OIH have clinical relevance?
   - Yes

Summary

6. Is there an association between OIH and gender, age and addiction?
   - To date, there are no studies which have had gender or age as a primary outcome variable. Opioid maintained individuals demonstrate OIH using the cold pressor test but hyperalgesia appears to resolve when maintenance therapy is discontinued and the individuals remains drug free.

Questions