

# Effectiveness of opioids for chronic pain—the SPACE trial in context

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# Disclosure

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- No commercial financial relationships
- Research funding from VA, NIH, & PCORI
- Views expressed in this presentation do not reflect the position or policy of the US government

# Poll question

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- What is your primary role related to opioid prescribing for chronic pain?
  - Prescribing clinician
  - Non-prescribing clinician
  - Researcher
  - Student
  - Other

# Definition of chronic pain

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- Persistent or recurrent pain for > 3-6 months
  - 20-30% of US adults (~40-100 million)
- “High impact chronic pain” = persistent or recurrent pain causing activity limitations/participation restrictions
  - 4.8% of US adults (~10.6 million)

# Treatments for chronic pain

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- Some treatments target disease-specific factors
  - Example: joint replacement in severe osteoarthritis
- Most treatments target common pathways involved in pain sensation, pain maintenance, pain amplification, or pain-related disability
  - Example: exercise therapy → body mechanics, strength, activity tolerance, fear of movement
  - Example: opioid therapy → mu receptors that modulate transmission of pain signals

JAMA | Original Investigation

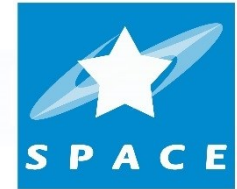
# Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain

## The SPACE Randomized Clinical Trial

Erin E. Krebs, MD, MPH; Amy Gravelly, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

- Opioid therapy was not superior to non-opioid medication therapy for chronic back pain or hip or knee osteoarthritis pain over 12 months

# Background



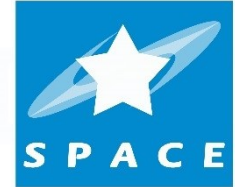
## *EVIDENCE TABLE*

	Recommendations	Sources of Evidence
1	Opioid therapy is indicated for moderate to severe pain that has failed other indicated therapeutic interventions	Breivik, 2001
2	Consider the ethical imperative of benefit-to-harm profile	Joranson et al., 2002 Laval et al., 2002

*LE=Level of Evidence; QE = Quality of Evidence; SR = Recommendation (See Appendix A)*

# Strategies for Prescribing Analgesics Comparative Effectiveness Trial

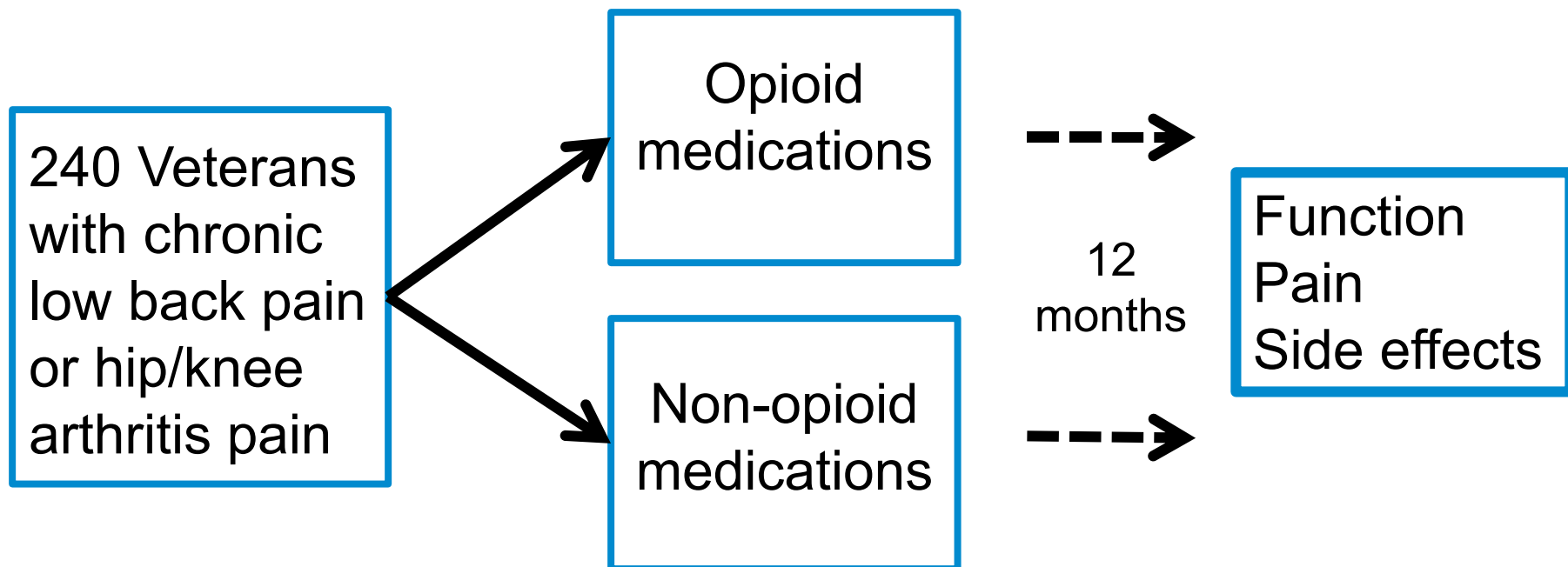
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Objective: To compare benefits & harms of opioid therapy vs. non-opioid medication therapy over 12 months among patients with *chronic moderate-severe back or osteoarthritis pain despite analgesic use*

Design: Pragmatic randomized trial with blinded outcome assessment





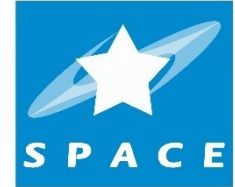
ClinicalTrials.gov: NCT01583985

Funded by VA Health Services Research & Development IIR 11-125

Krebs EE, et al. JAMA. 2018;319(9):872-882

# Eligibility

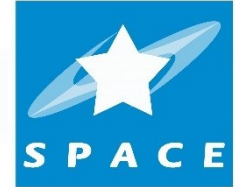
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- Inclusion criteria
  - Chronic back pain or hip/knee OA pain
  - Moderate-severe pain severity and functional interference despite analgesic use
- Major exclusion criteria
  - Current long-term opioid therapy
  - Absolute contraindications to opioid therapy
- No exclusion for severe PTSD/depression, serious medical conditions, or past SUD

# Interventions

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- All patients received individualized medication management within assigned group
  - Telecare collaborative management (clinical pharmacist care manager)
  - Treatment to target individual functional goals and improvement in PEG score
  - Prescribing strategy with 3 medication steps

# Prescribing strategies

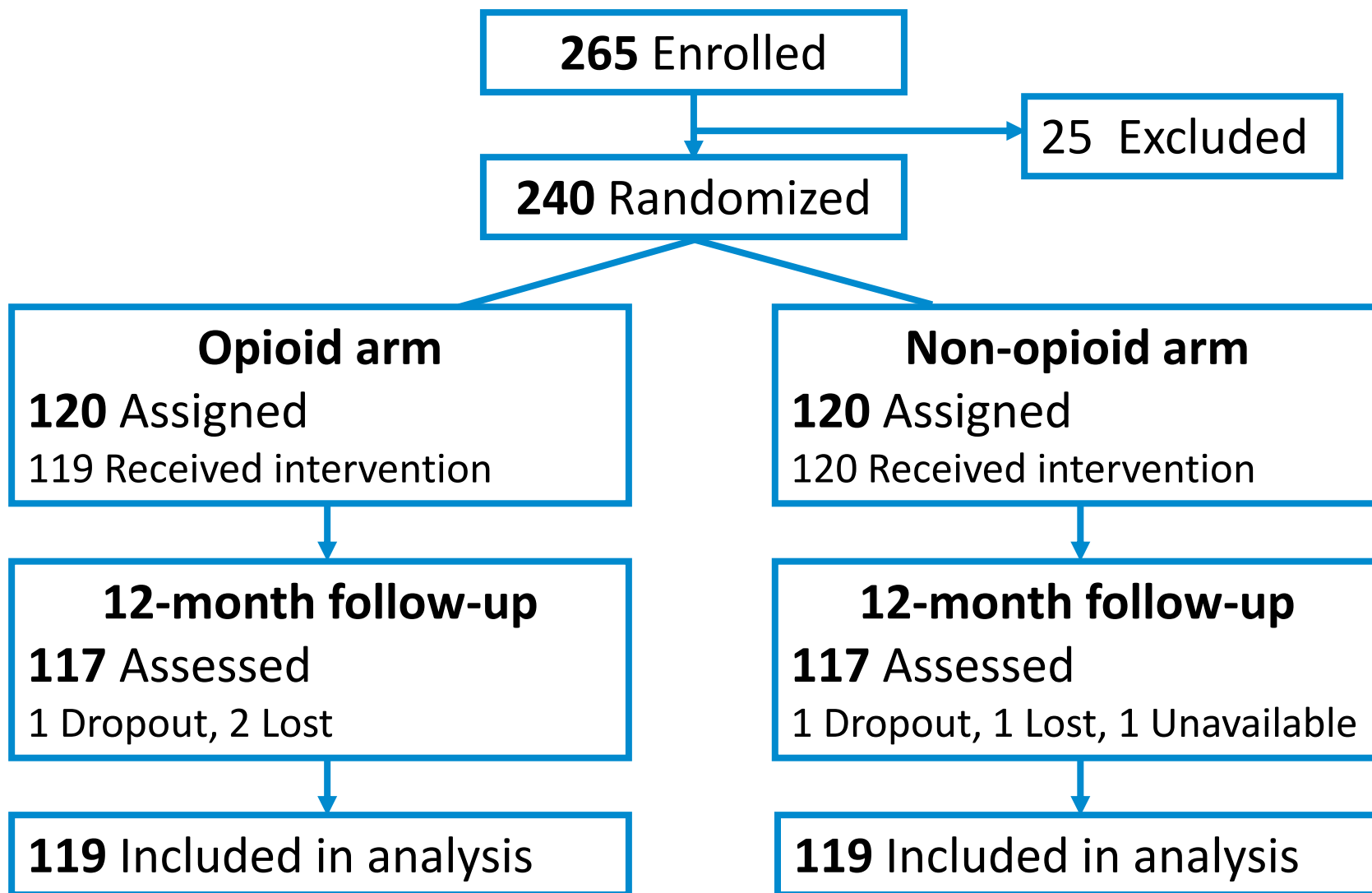


**Table: Medications within each treatment group**

	<b>Opioid group</b>	<b>Non-opioid group</b>
<b>Step 1</b>	Morphine IR* Oxycodone IR Hydrocodone/APAP	Acetaminophen* Oral NSAIDs Topical diclofenac
<b>Step 2</b>	Morphine SR Oxycodone SA	Nortriptyline, amitriptyline Gabapentin Topical lidocaine, capsaicin
<b>Step 3</b>	Fentanyl transdermal	Pregabalin Duloxetine Tramadol

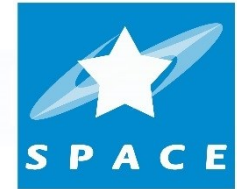
Opioid dose limited to 100 ME mg/day

\* Preferred initial selection



# Participant characteristics

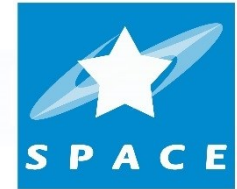
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	<b>Opioid (n=120)</b>	<b>Non-opioid (n=120)</b>
Age, mean years	56.8	59.7
Women, %	13	13
Primary back pain	65	65
Primary hip/knee OA pain	35	35

# Preferences & perceptions

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n=240

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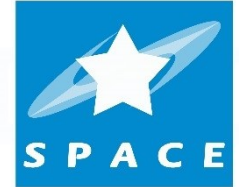
## Arm preference before randomization

Unsure/no preference	51%
Opioids	29%
Non-opioids	20%

## Perceptions of treatment arms,\* mean (SD)

Opioid effectiveness	7.8 (2.0)
Non-opioid effectiveness	5.7 (2.7)

\*Rated from 0 “not at all effective” to 10 “most effective possible”

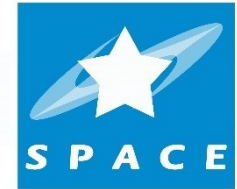


*“There’s a reason it’s controlled—usually because it’s better. So in my mind, when you’re in serious pain, you need serious medication.”*

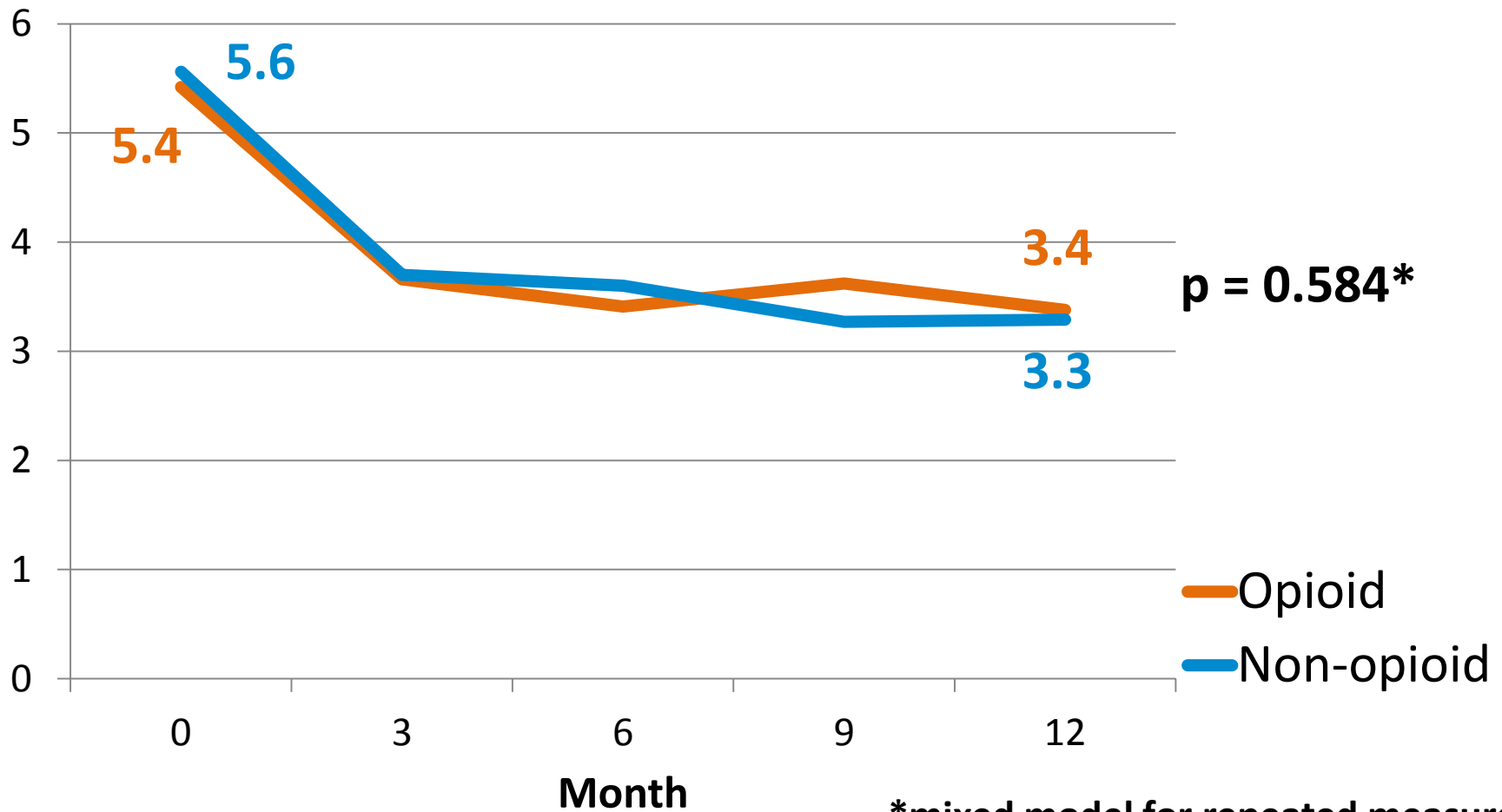
- Study participant on reason for opioid arm treatment preference



# Pain interference with function



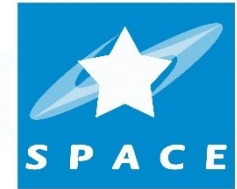
Mean BPI Interference (n=238)



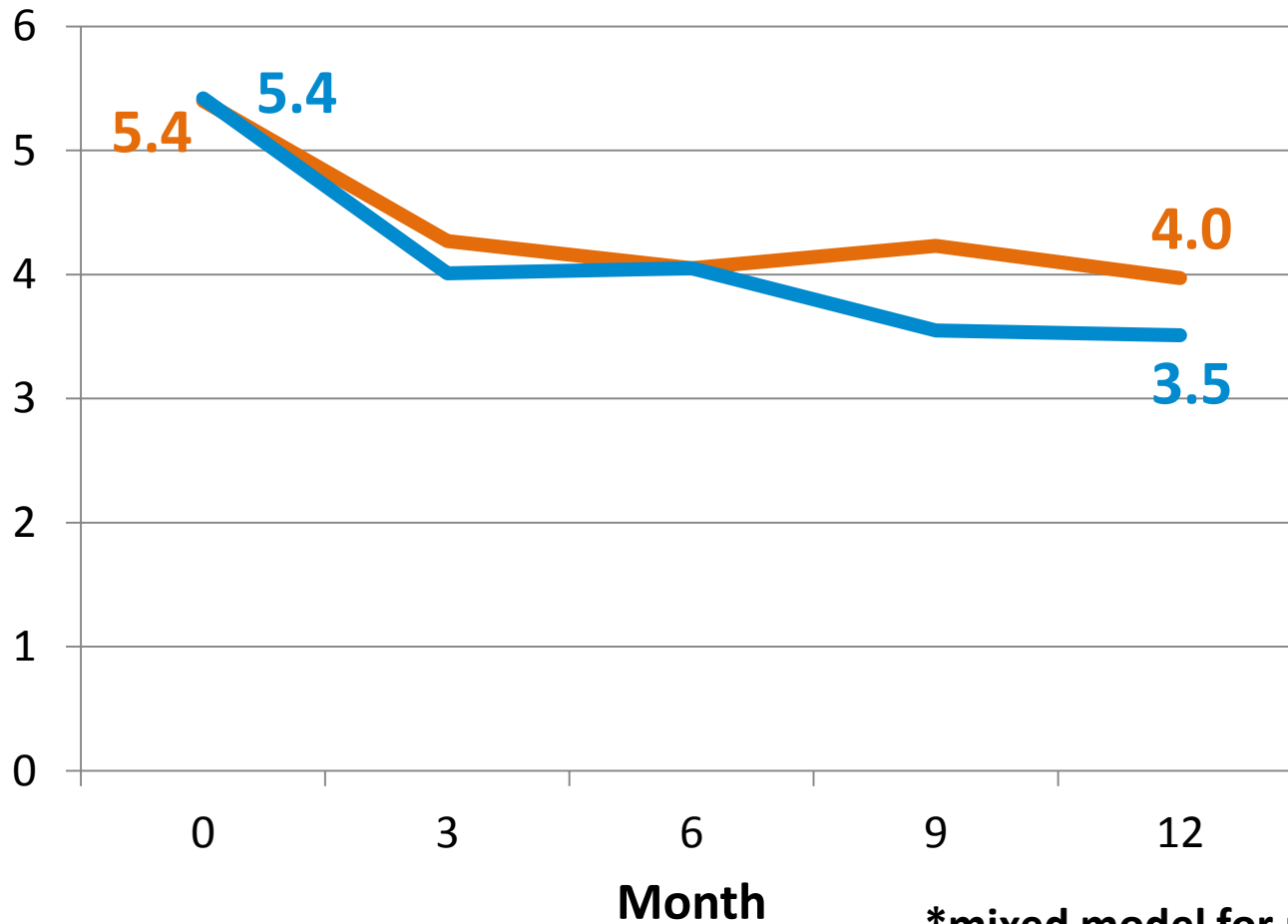
p = 0.584\*

\*mixed model for repeated measures

# Pain intensity



Mean BPI Severity (n=238)

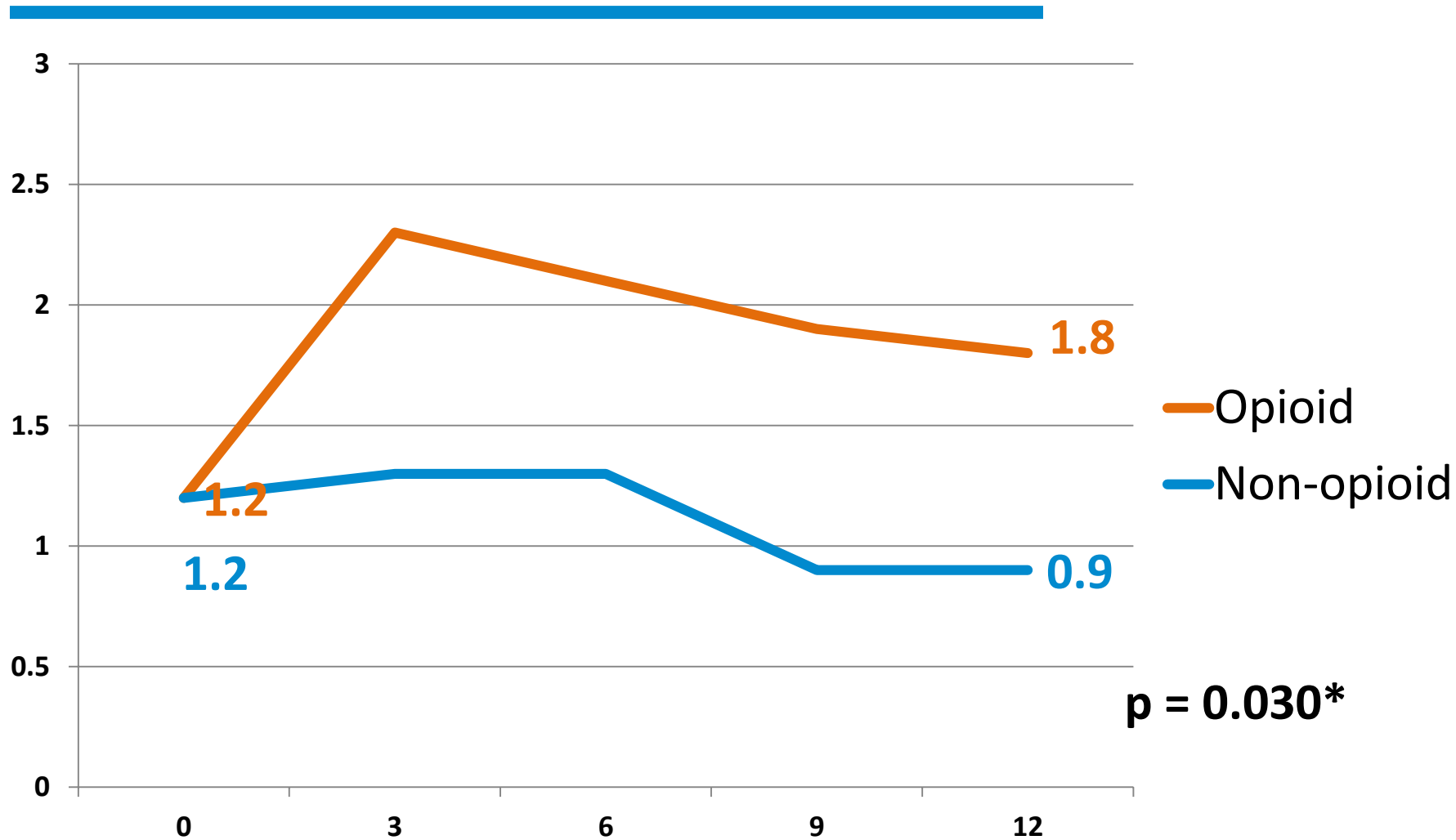
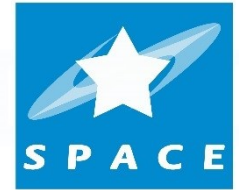


$p = 0.034^*$

— Opioid  
— Non-opioid

\*mixed model for repeated measures

# Medication side effects



\*treatment x time interaction

# Adverse events

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- No difference between groups in rates of ED visits or hospitalizations
- Each group had 1 analgesic-related ED visit or hospitalization
- No death, addiction, or diversion events



*I'm glad I'm not on opiates anymore. They were effective, but it felt like I was living my life in a sleepy stupor. I did not like being tired and, you know, I could lay down on the floor and fall asleep. My quality of life, I thought, diminished because of the opiates.*

– Study participant (opioid responder)

# Results summary

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- Opioid therapy was not superior to non-opioid medication therapy over 12 months
  - No difference in pain-related function
  - Non-opioids → slightly better pain intensity
  - Non-opioids → fewer bothersome side effects

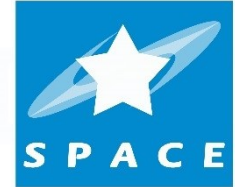
# Implication #1

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- Results do not support initiation of long-term opioid therapy in patients with moderate-severe pain despite analgesic use

# Implication #2



- Results do support active non-opioid medication management in patients with moderate-severe pain despite analgesic use

## Patients with clinically significant improvement (defined as 30% reduction from baseline)

	Opioid group	Non-opioid group
<b>BPI interference</b>	69 (59.0%)	71 (60.7%)
<b>BPI severity</b>	48 (41.0%)	63 (53.9%)



Original Investigation

# Telecare Collaborative Management of Chronic Pain in Primary Care

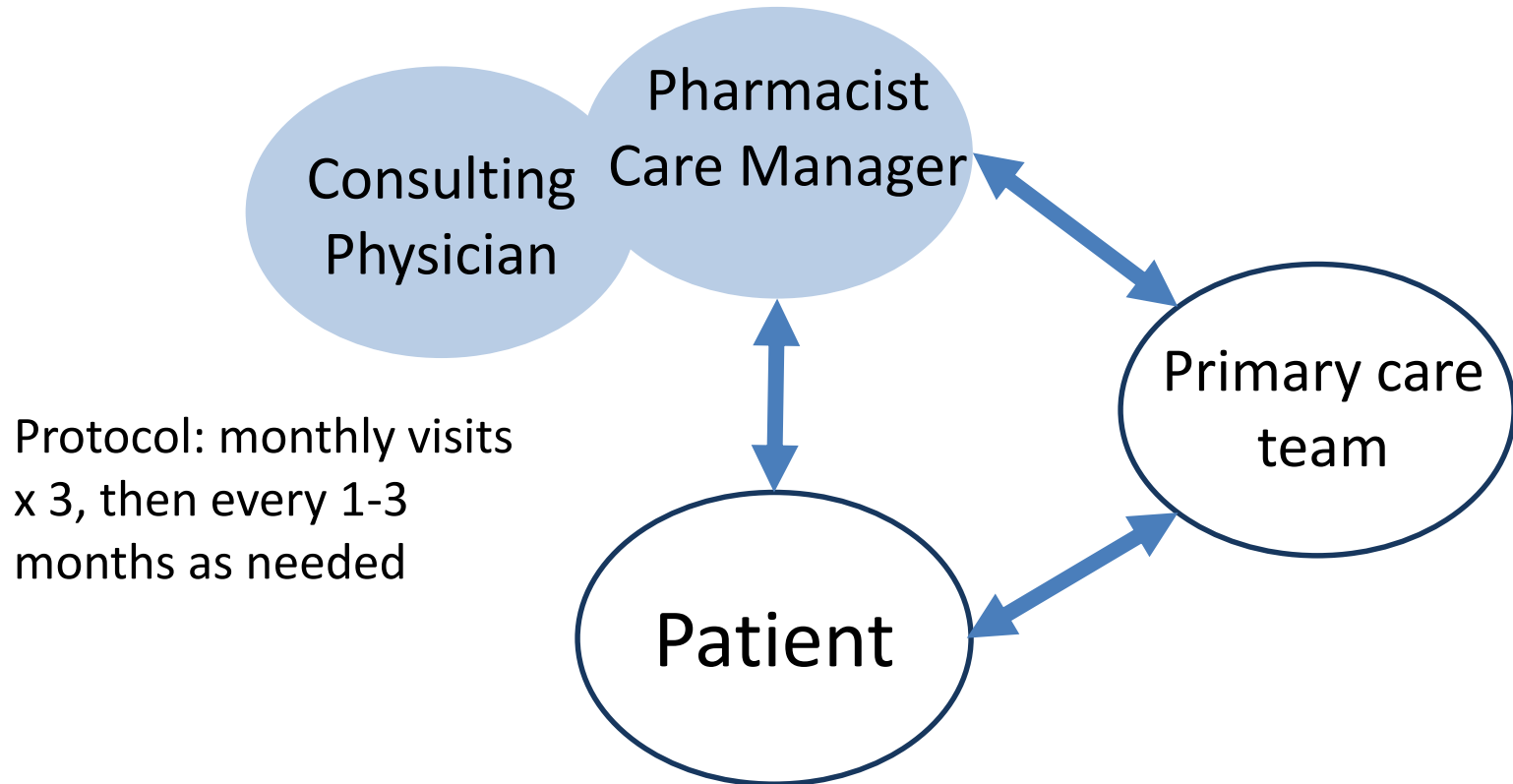
## A Randomized Clinical Trial

Kurt Kroenke, MD; Erin E. Krebs, MD; Jingwei Wu, MS; Zhangsheng Yu, PhD; Neale R. Chumbler, PhD;  
Matthew J. Bair, MD

- SPACE care model based on effective model from prior randomized trial (PI Kurt Kroenke)
  - Clinical response: 52% for telecare collaborative management vs. 27% usual care (NNT 4.1)
- 3 key features: Care manager with expert back-up; structured reassessment; stepped approach to analgesic management

# Feature 1: Pharmacist care manager

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Mean number of visit over 12 months = 9 (3 in clinic, 6 telephone)

# Feature 2: Structured reassessment

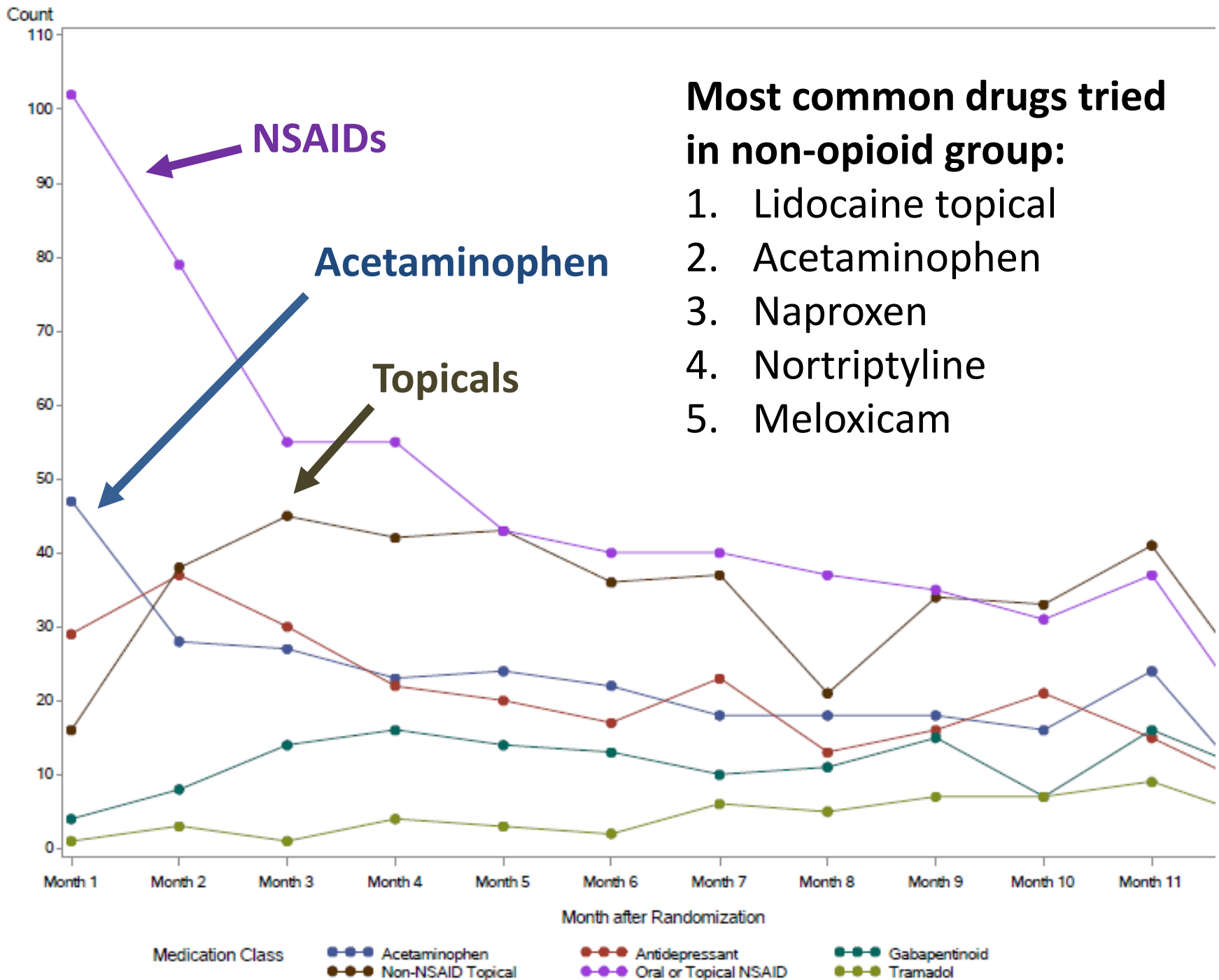
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- Progress toward individual functional goals
- Pain (PEG)
  - **PEG:** Past week rating of...
    - **Pain** on average
    - Pain interference with **enjoyment** of life
    - Pain interference with **general** activity
- Depression (PHQ-2)
  - **PHQ-2:** Frequency in past 2 weeks of...
    - Feeling down depressed or hopeless
    - Little interest or pleasure in doing things
- Anxiety (GAD-2)
  - **GAD-2:** Frequency in past 2 weeks of...
    - Feeling nervous, anxious, on edge
    - Unable to stop or control worrying

# Feature 3: Stepped analgesics

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- VA formulary medications in 3 steps
  - Actively trialed
  - Discontinued if not effective or tolerated
- Shared decision-making approach based on preferences and change in follow-up measures
- Patients in nonopioid group trialed median of 4 drugs over 12 months



**Opioids for chronic pain**

**CONTEXT**

# What we knew before SPACE

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- Evidence from short-term placebo-controlled trials: opioids decrease pain slightly more than placebo
  - Chronic back pain:  $\Delta$  ~10 points on 0-100 scale
  - Hip/knee osteoarthritis:  $\Delta$  ~7 points on 0-100 scale
- Evidence gaps
  - Opioids compared to active treatment
  - Opioid effectiveness > 3 months



# Updated meta-analysis

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JAMA | Original Investigation

## Opioids for Chronic Noncancer Pain A Systematic Review and Meta-analysis

Jason W. Busse, DC, PhD; Li Wang, PhD; Mostafa Kamaleldin, MB BCh; Samantha Craigie, MSc; John J. Riva, DC, MSc; Luis Montoya, DDS, MSc; Sohail M. Mulla, PhD; Luciane C. Lopes, ScD, MSc; Nicole Vogel, PhD; Eric Chen, BHSc; Karin Kirmayr, MD; Kyle De Oliveira, MD; Lori Olivieri, MD; Alka Kaushal, MBBS, DA; Luis E. Chaparro, MD; Inna Oyberman, MD; Arnav Agarwal, MD; Rachel Couban, MA, MIST; Ludwig Tsoi, MBChB; Tommy Lam, MBBS; Per Olav Vandvik, MD, PhD; Sandy Hsu, BA; Malgorzata M. Bala, MD; Stefan Schandelmaier, MD; Anne Scheidecker, MD; Shanil Ebrahim, PhD; Vahid Ashoorion, MD, PhD; Yasir Rehman, MD, MSc; Patrick J. Hong, BMSc; Stephanie Ross, PhD; Bradley C. Johnston, PhD; Regina Kunz, MD, MSc; Xin Sun, PhD; Norman Buckley, MD; Daniel I. Sessler, MD; Gordon H. Guyatt, MD, MSc

- Reviewed RCTs of opioid vs. nonopioid control for chronic pain (excluded if follow-up < 4 weeks)
  - Included 96 RCTs of 1-6 months' duration



# Opioids for Chronic Noncancer Pain

## A Systematic Review and Meta-analysis

- Opioids were slightly better than placebo
  - Pain:  $\Delta$  ~0.8 points on 0-10 scale
  - Physical function:  $\Delta$  ~2 points on 0-100 scale
- Opioids had smaller effects on pain in studies with longer follow-up
- No relationship between dose and pain/function
- Opioids did not differ from NSAIDs (9 trials)

*What about patients already  
on long-term opioids\*?*

\*excluded from SPACE trial

# Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

## A Systematic Review

Joseph W. Frank, MD, MPH; Travis I. Lovejoy, PhD, MPH; William C. Becker, MD; Benjamin J. Morasco, PhD; Christopher J. Koenig, PhD; Lilian Hoffecker, PhD, MLS; Hannah R. Dischinger, BS; Steven K. Dobscha, MD; and Erin E. Krebs, MD, MPH

- 67 studies that reported outcomes of opioid reduction or discontinuation were included
  - Designs: 11 randomized trials, 56 observational studies (8 controlled, 48 uncontrolled)
  - Interventions: 31 interdisciplinary pain programs, 10 buprenorphine, 6 behavioral...

# Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

## A Systematic Review

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- Interdisciplinary pain programs and behavioral interventions may be effective in reducing opioid dose
- Pain, function, & quality of life may improve during and after opioid dose reduction
- **\*\*Overall, very low quality of evidence\*\***

# Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

## A Systematic Review

Joseph W. Frank, MD, MPH; Travis I. Lovejoy, PhD, MPH; William C. Becker, MD; Benjamin J. Morasco, PhD; Christopher J. Koenig, PhD; Lilian Hoffecker, PhD, MLS; Hannah R. Dischinger, BS; Steven K. Dobscha, MD; and Erin E. Krebs, MD, MPH

- Considerations
  - Findings apply to patients who agreed to participate
  - Inadequate evidence about risks/adverse effects of tapering
  - **\*\*Promising interventions were intensive, involving close follow-up and, in most cases, interdisciplinary support\*\***

# Conclusions

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- SPACE found no advantage of opioids over nonopioid therapy among patients who previously “failed” nonopioid therapy for chronic pain
- Results are consistent with other evidence
  - Opioids have small benefits that diminish over time and are not related to dose
  - Opioids not superior to other analgesic medications

# Conclusions

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- SPACE results support current opioid guidelines
  - CDC: non-drug therapies and non-opioid medications are preferred over opioids
  - VA/DoD: recommends against initiating long-term opioids for chronic pain
- SPACE results do not apply to patients already on long-term opioids
  - Evidence for opioid reduction/discontinuation is low-quality, so tapering should be cautious, individualized, and collaborative

# Bonus slide...

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# Medications are not the first or best treatments for chronic pain

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## Psychological therapies

Cognitive Behavioral Therapy for Pain (CBT-P)

Acceptance & Commitment Therapy (ACT)

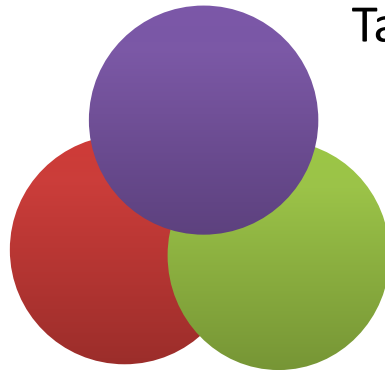
Mindfulness-Based Stress Reduction (MBSR)

## Movement therapies

Individual and group exercise (aerobic, resistance, coordination/stabilization, etc.)

Yoga

Tai Chi



## Manual therapies

Acupuncture

Manipulation

Massage



# Credit and thanks to...

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- **Our Veteran participants**
- **My primary care colleagues**
- Best Paper co-authors: Amy Gravely, Sean Nugent, Agnes Jensen, Beth DeRonne, Lizzy Goldsmith, Kurt Kroenke, Matt Bair, Siamak Noorbaloochi
- SPACE clinicians: Beth DeRonne, EJ Jones, Melissa Bell, Doug DeCarolis, Howard Fink, Steven Fu
- SPACE research team members: Indulis Rutks, David Leverty, Ruth Balk, Erin Linden, Andrea Cutting, Melvin Donaldson, Preetanjali Thakur, Marianne Matthias

## Questions?

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