The SPACE Trial

Is This What We've Been Waiting For?

The First Randomized Trial of Opioid Therapy Reporting Long-Term Pain, Function, and Quality of Life Outcomes

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Panelists: Elizabeth Powers, MD; Joel Rice, MD; David Ebel, RPT

Moderator: Chuck Hofmann, MD

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

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*Strategies for Prescribing Analgesics Comparative Effectiveness

Study Design

Clinical Characteristics of Eligible Patients

- Minneapolis VA System
- Moderate to Severe Chronic (pain nearly every day for 6 or more months) back pain or hip or knee osteoarthritic pain
- Patients on benzodiazepines and/or long-term opioids excluded
- Patients with substance abuse disorder excluded
- Average age 57 yrs Opioid Group, 60 yrs Nonopioid Group
- 78 patients with back pain and 42 patients with hip or knee osteoarthritis pain in each group
- 13% women in each group
- 88% white in Opioid Group, 86% in Nonopioid Group

Randomization

- Stratified by primary pain diagnosis to ensure balanced numbers (120 in each group)
- Following randomization, pharmacy staff, patient, and provider informed of group assignment

Study Design (con't)

Interventions

- Opioid Prescribing Strategy
  - Step 1: Hydrocodone/APAP, Oxycodone, or Morphine IR
  - Step 2: Oxycodone or Morphine SA
  - Step 3: Transdermal Fentanyl
  - If no response by MED 60, rotation to a different opioid before dose escalation
  - Fewer than 15% of patients had an average MED of 50 or more
  - Maximum MED = 100

- Nonopioid Prescribing Strategy
  - Step 1: APAP + NSAID
  - Step 2: Step 1 + TCA/Gabapentin/Topical capsaicin/lidocaine
  - Step 3: Step 1 + Pregabalin/duloxetine/tramadol (13 patients)

Study Design (con't)

Outcome Measurements

- Primary Outcomes
  - Pain-related functions (7 item Brief Pain Inventory interference scale)
  - Pain intensity (4 item Brief Pain Inventory severity scale)
  - Adverse Outcomes checklist of 10 medication-related symptoms
- Secondary Outcomes
  - Quality of Life (Veterans RAND 12 item Health Survey – VR-12)
  - Pain Related Physical Function (11 item Roland-Morris Disability Questionnaire – RMDQ)
  - Patient Health Questionnaire – PHQ-8
  - Generalized Anxiety Disorder measure – GAD-7
  - Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance short form
  - Migraine Disability Assessment (MIDAS) Questionnaire
  - Arizona Sexual Experience Scale (ASEX)
  - Multidimensional Fatigue Inventory Scale (MFI)

Results

Pain Related Function

- Most patients in both Groups improved but there were no significant differences between the two groups over 12 months

Pain Intensity

- Significantly better in the Nonopioid Group over 12 months

Adverse Outcomes

- Significantly more medication-related outcomes in the Opioid Group over 12 months

Key Points

- **Question**

  - For patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use, does opioid medication result in better pain-related function?

- **Findings**

  - In this randomized clinical trial that included 240 patients, the use of opioid vs. nonopioid medication therapy did not result in significantly better pain-related function over 12 months.

- **Conclusion**

  - This study does not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Non-pharmacologic Treatments

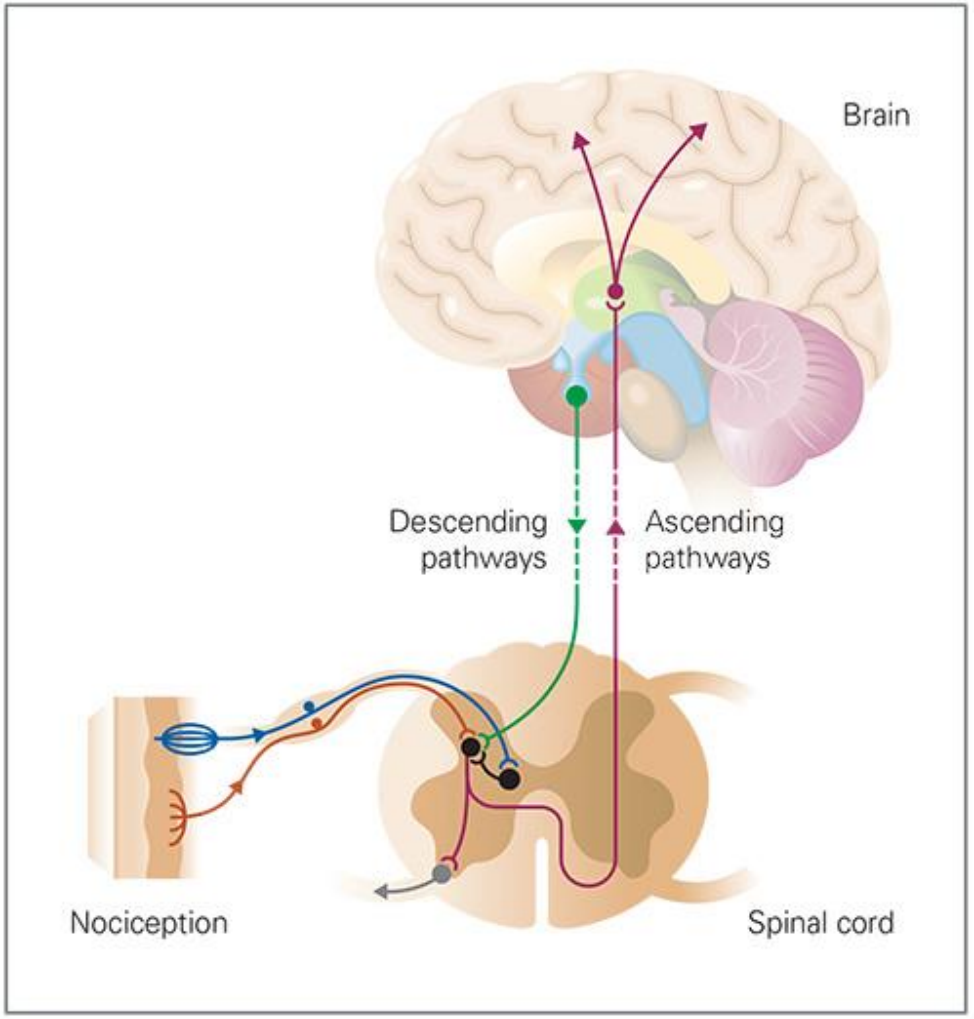
Patient-reported co-interventions during the study year*

Treatment, n (%)	Opioid group (n=106)	Non-opioid group (n=105)
Acupuncture	7 (7)	9 (9)
Biofeedback	1 (1)	2 (2)
Chiropractic or osteopathic manipulation	24 (23)	15 (14)
Homeopathy or naturopathy	2 (2)	2 (2)
Hypnosis	0	0
Nutritional advice of counseling	11 (10)	13 (12)
Massage	20 (19)	25 (24)
Mental health counseling or therapy	15 (14)	14 (13)
Personal training or supervised exercise therapy	18 (17)	19 (18)
Physical therapy	39 (37)	25 (24)
Injections in spine, such as epidurals or facet blocks	9 (9)	8 (8)
Injections in the knee, hip, or other joints	29 (28)	23 (22)
Surgery for spine (neck or back)	1 (1)	1 (1)
Surgery for knee or hip, such as arthroscopy or joint replacement	3 (3)	8 (8)

*Non-pharmacological therapies were allowed and not managed by the study.
Patients were asked “In the past 12 months since you started the study, have you seen a provider or practitioner for any of the following therapies to manage pain?” Numbers are those responding “yes, during the past year.”

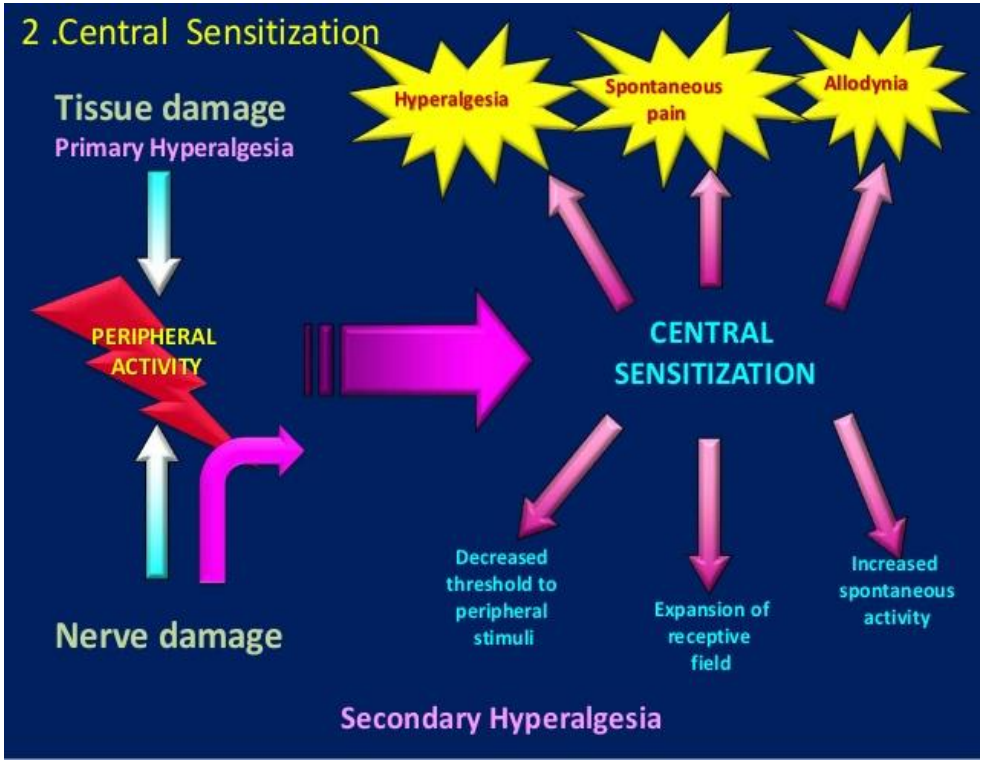
Perception of Pain

- Perception Components
  - Nociception: Signal to brain
  - Neuromodulation: Regulation of that signal.
    - Thresholds of signals can be modified
    - Other nerve pathways can be “recruited”
    - Emotional and psychosocial components contribute



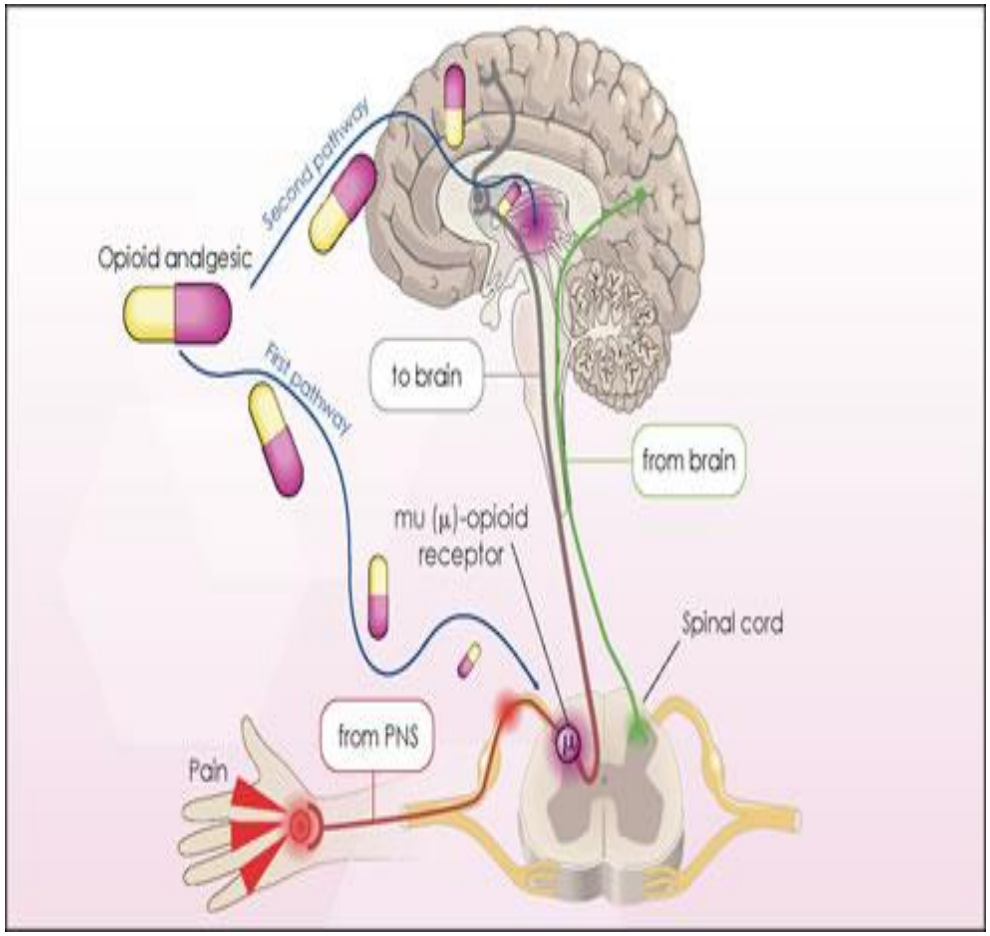
Neuromodulation and Central Sensitization

The nervous system can go through a wind-up process and become regulated into a **persistent state of high reactivity.**



Opioid Tolerance and Opioid–Induced Hyperalgesia (OIH)

- Opioids are a double-edged sword characterized by the loss of efficacy overtime combined with habituation.
- Some people who receive opioids for the treatment of pain may develop OIH where they could become more sensitive to certain painful stimuli despite the absence of disease progression



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ANOTHER PIECE IN THE PUZZLE IN TREATING CHRONIC PAIN

DAVID EBEL, PT

DNRS: DYNAMIC NEURAL RETRAINING SYSTEM

- Research over the past 20 years has shown that the brain is a major component in chronic pain and that the brain can be changed. This is called neuroplasticity. (SEE BOOKS BY DR. NORMAN DOIDGE, MD)
- Neuroplasticity is an approach to pain management that empowers the patient "to do their part" as Hippocrates suggested. **Neuroplasticity is the active involvement of the whole patient: mind (thoughts), brain (physical structure; i.e. neurons etc.), and body in their recovery from chronic pain.** It searches for areas; healthy mind, brain and body that may aid in recovery, while acknowledging the pain and deficits experienced by the patient.

Acupuncture

- A 2008 study published in *Spine* found "strong evidence that acupuncture can be a useful supplement to other forms of conventional therapy" for low back pain. After analyzing 23 clinical trials with a total of 6,359 patients, the study authors also found "moderate evidence that acupuncture is more effective than no treatment" in relief of back pain. The authors note that more research is needed before acupuncture can be recommended over conventional therapies for back pain.
- Just how does acupuncture work? According to traditional Chinese medicine, pain results from blocked energy along energy pathways of the body, which are unblocked when acupuncture needles are inserted along these invisible pathways. Acupuncture may release natural pain-relieving opioids, send signals to the sympathetic nervous system, and release neurochemicals and hormones.

Massage Therapy

- In a 2009 research review published in *Spine*, researchers reviewed 13 clinical trials on the use of massage in treatment of back pain.

The study authors concluded that massage "might be beneficial for patients with subacute and chronic nonspecific low back pain, especially when combined with exercises and education." Noting that more research is needed to confirm this conclusion, the authors call for further studies that might help determine whether massage is a cost-effective treatment for low back pain.

Massage therapy may also alleviate anxiety and depression associated with chronic pain.

- Nutrition and Dietician consultations
  - Anti-inflammatory diets and diets that effect digestion have been found to have a significant impact on chronic pain.

Vitamin D

- Chronic muscle pain can be a symptom of vitamin D deficiency. What's more, some research suggests that treatment with vitamin D supplements may lead to clinical improvement in back pain symptoms among people with low initial concentrations of vitamin D, according to a 2005 report published in the *British Medical Journal*.

Yoga

- Yoga creates balance in the body through various poses that develop flexibility and strength. Restorative yoga is gentle and a very good starting point for patient's in chronic pain.

Physical Therapy which includes manual techniques and exercise

- Exercise:
  - Aqua Therapy is a gentle way to work with using the buoyancy and gentle resistance of water to restore movement and strength.
  - Being active releases pressure on intervertebral disks, taking pressure off of the spinal nerve roots. Regular exercise is extremely important. Begin with a gentle prescribed workout routine that strengthens muscles specific to the patient's needs.
- Manual Techniques:
  - CranioSacral Therapy
  - Myofacial Release Therapy
  - Visceral Mobilization
  - Strain Counterstrain Techniques
  - Lymph Drainage
  - Somato-emotional Release Techniques
  - Postural Retraining
  - Mechanical Link Technique

Balneotherapy

- One of the oldest therapies for pain relief, balneotherapy is a form of hydrotherapy that involves bathing in mineral water or warm water including dead sea salts, Epsom salts baking soda and essential oils.

Meditation

- An ancient mind-body practice, meditation has been found to increase pain tolerance and promote management of chronic pain in a number of small studies. In addition, a number of preliminary studies have focused specifically on the use of meditation in management of low back pain. A 2008 study published in *Pain*, for example, found that an eight-week meditation program led to an improvement of pain acceptance and physical function in patients with chronic low back pain. The study included 37 older adults, with members meditating an average of 4.3 days a week for an average of 31.6 minutes a day.

Vitamin B12

- A study published in the *European Review for Medical and Pharmacological Sciences* in 2000 examined the safety and effectiveness of vitamin B12 injections for low back pain. Involving 60 patients, the study found that those who received vitamin B12 injections experienced a statistically significant reduction in pain and disability. They also used less pain medication than those who received a placebo.

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- Norman Doidge, MD; "The Brain That Changes Itself"
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- Jeffrey M. Schwartz, MD; "The Mind and the Brain: Neuroplasticity and the Power of Mental Force"
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