Opioid vs Nonopioid Medications on Pain-Related Function in Chronic Pain (Back, OA-Hip/Knee)

Critical Appraisal & Insights from the SPACE RCT [1,2]

BOTTOM LINE ⇒ supports a nonopioid dominant step approach to long-term management of moderate-severe CNCP

- Patients with chronic non-cancer pain (CNCP) – (back pain or osteoarthritis of the hip or knee) did as well or better on a strategy that favored a non-opioid stepped approach to therapy compared to an opioid stepped approach (relatively low-dose).
  - No difference in functional outcomes
  - Pain intensity was worse in the opioid strategy arm than the non-opioid arm (NNH = 8)
  - Adverse events were more common in the opioid strategy arm
- Significant improvements in both pain and function was seen in both groups, possibly related to both being allowed the same access to non-pharmacologic interventions, and both had frequent follow-up visits and/or phone calls.
- Patients in the opioid group saw a greater reduction in anxiety score
- Contextualizing requires consideration for a) lack of patient blinding b) limited CNCP indications included, c) low MED/day 85% <50MED

BACKGROUND [1]

- Long-term opioid therapy has been a common approach for managing moderate-severe chronic musculoskeletal pain.
- Quality RCT evidence to evaluate the comparative long-term (>3-6 month) benefits and harms has been lacking

TRIAL BACKGROUND/DESIGN [1]

DESIGN: randomized, outcome assessors blinded but was not possible to mask patients; allocation concealed; 12 month duration; pragmatic trial design {diverse patients in primary care, flexibility in medication selection and dose, participation in non-pharmacological pain therapy encouraged. Funded by Veterans Affairs (VA)}.

INTERVENTION in addition to optional non-pharmacological treatments:

A) Opioid Prescribing Strategy - 3 step: **i)** morphine IR, hydrocodone/acetaminophen and oxycodone IR; **ii)** morphine sustained action (SR) and oxycodone SR **iii)** transdermal fentanyl. Single opioid preferred, but SR + IR was considered based on patient. Doses titrated up to 100 MED/day; if no response to 60 MED/day, rotation to another opioid was considered.

B) Non-Opioid Prescribing Strategy – 3 step: **i)** acetaminophen and NSAIDs; **ii)** adjuvant oral medications (nortriptyline, amitriptyline, gabapentin) and topical analgesics (capsaicin lidocaine); **iii)** pregabalin, duloxetine and tramadol. Changes included titrating, replacing or adding medications.

INCLUSION: veterans with chronic back or hip/knee osteoarthritis pain, with moderate-severe intensity and interference with function despite analgesics. (BPI: pain ≥ 5 on a 0-10 scale; interference with function ≥ 5)

EXCLUSION: a) schizophrenia, bipolar or other psychosis; b) moderately severe cognitive impairment, c) anticipated back, knee or hip surgery within 12 months; d) those receiving current chronic opioid therapy or absolute contraindications to either strategy. (e.g. substance use disorder)

POPULATION at baseline: n=240

- Mean age ~58; 87% male; ~87% white; education: 25% ≥4yr degree; veterans affairs population
- Employed for wages: 42% vs 26%; retired: 36% vs 47%; 65% back pain & 35% OA, hip or knee
- Similar mental health, ~22% depression; 11% anxiety; 21% PTSD (severe depression and PTSD excluded)

RESULTS

follow-up: median 277 days (9.2 months)

TABLE 1: EFFICACY (MODIFIED ITT ANALYSIS)

CLINICAL ENDPOINTS	OPIOID STRATEGY n=119	NONOPIOID STRATEGY n=119	BETWEEN GROUP DIFFERENCE	P VALUE*	NNT / NNH 12 MONTHS	COMMENTS
PRIMARY EFFICACY ENDPOINT						
Pain-related function (BPI 7 item)	5.4 ⇒	5.5 ⇒	-0.1	.58 (no signif. difference)		NO DIFFERENCE SEEN **BPI: 0-10 scales: higher score = worse** **Minimum clinically important difference: (MCID):** 1-point difference as the MCID for BPI interference and BPI severity, and used a 30% reduction from baseline as MCID for moderate improvement
- 3mo	3.7	3.7	0.0			
- 6mo	3.4	3.6	-0.2			
- 9mo	3.6	3.3	0.4			
- 12 mo	3.4	3.3	0.1			
SECONDARY EFFICACY ENDPOINTS						
PAIN INTENSITY (BPI 4-ITEM) – 12 MO	5.4 ⇒ 4.0	5.4 ⇒ 3.5	**0.5**	.03		
PAIN INTENSITY ≥ 30% IMPROVEMENT	41.0%	53.9%	**12.8%**	.05	**8**	OPIOIDS WORSE than non-opioid strategy for pain in 1 of every 8 people treated @12 mo
Functional response ≥ 30% improvement	59%	60.7%	-1.7%	.79	-	
VR-12 Physical health – 12 mo	27.2 ⇒ 32.7	27.0 ⇒ 33.9	-1.3	.23		0-100; lower score = worse
VR-12 Mental health – 12 mo	47.3 ⇒ 51.2	47.8 ⇒ 50.4	0.7	.40		
PHQ-8 Depression symptom – 12 mo	6.3 ⇒ 4.3	5.8 ⇒ 4.5	-0.2	.13		0-24; higher score = worse
GAD-7 ANXIETY SYMPTOM – 12 MO	4.0 ⇒ 2.5	3.5 ⇒ 2.8	-0.4	.02		0-12; higher score = worse (OPIOID BETTER)
PROMIS Sleep Disturbance – 12 mo	25.5 ⇒ 23.4	24.2 ⇒ 21.0	2.3	.33		8-32; higher score = worse
MIDAS Headache – 12 mo	6.1 ⇒ 3.7	6.1 ⇒ 3.2	0.5	.82		0-270; higher score = worse
ASEX Sexual function – 12 mo	17.4 ⇒ 17.9	17.7 ⇒ 19.0	-1.1	.49		5-30; higher score = worse
MFI General fatigue – 12 mo	13.8 ⇒ 12.5	12.8 ⇒ 12.0	0.6	.68		4-20; higher score = worse
MFI Reduced motivation – 12 mo	9.8 ⇒ 8.6	8.8 ⇒ 8.8	-0.2	.09		4-20; higher score = worse
Other patient-reported outcomes included & not significant difference: MFI physical fatigue, MFI reduced activity						
PRIMARY ADVERSE OUTCOME						0-19; higher score = worse
Medication-related symptom checklist	1.2 ⇒ 1.8	1.2 ⇒ 0.9	0.9	0.3		
SECONDARY ADVERSE OUTCOMES & POTENTIAL MISUSE MEASURES						11 illicit drug positives in nonopioid group vs 5 in opioid group (p=0.13) Higher discontinuation rate in opioid group (23 vs 10) Supplement 2
Hospitalization, all cause ED visits, falls; MISUSE: positive UDS, misuse behaviour, patient reported substance use						

*P value not adjusted for multiple testing

STRENGTHS, LIMITATIONS, UNCERTAINTIES & OF INTEREST

STRENGTHS:

- Included patients with mild-moderate depression and PTSD which are both common comorbidities in CNCP
- Step and "treat to target" approach reflects real life and recommended approaches to pain (pain intensity, enjoyment of life, general activity) [3]
- Reflects real life variation in adherence to medications
- Potential for reporting bias that should have favored opioids, strengthening our confidence that opioids underperformed
- Assesses opioid therapy at lower dosages which have become more recommended[3] (~85% opioid grp on <50 MED/day)

LIMITATIONS:

- Mostly Caucasian males
- Subjectivity of interventions and outcome reporting. Complexity of interventions precluded masking of patients and primary outcomes were patient reported.
- Limited in insights on higher opioid doses (≥ 50 MED); however, as doses increase there is unknown benefit and known harm (eg, opioid induced hyperalgesia, increased risk of fatal and non-fatal overdose)
- Does not represent and apply to patients with a significant history of using opioids for CNCP

UNCERTAINITIES:

- Study underpowered to detect small differences in most secondary outcomes
- Missing data from some endpoints could be enough to eclipse a statistically significant effect (e.g. not all patients reported on all measures at all follow-up visits)
- More patients in the opioid group had "unsure or no preference" regarding their treatment strategy assignment, compared to the non-opioid group (60% vs 43%). Could mean patients in the non-opioid group "cared more" or were more engaged in their therapy? This may represent a source of potential bias, especially given lack of patient blinding.
- Though a "long" study relative to other opioid studies, does not provide insight into longer-term toxicities of either strategies (eg, NSAIDs and CKD/CVD, opioids and hypogonadism)

OF INTEREST:

- Tramadol was included in Step 3 of NON-Opioid strategy, even though it has opioid activity
- TCA adequate trial defined as 50mg for 2+ weeks
- NSAID: diclofenac and etodolac not prescribed due to high CV risk
- Topical diclofenac was added mid-study when added to VA formulary
- LFTs rechecked within 3 months of starting diclofenac (if started)
- Initial opioid limit was 200 MED/day; changed/reduced mid-study
- Patients paid to participate (increased to $100 mid-study to increase recruitment)
- Of 4,485 with prior month health record of back or lower extremity pain, only 265 enrolled. 1,843 declined to participate and 2,377 did not meet pain diagnosis and severity criteria (common exclusions: fibromyalgia, migraine, opioid or benzo use, mental health condition and substance use disorder).
- FUNDED BY THE VA

BPI= brief pain inventory **MED/day**=morphine equivalent dose per day **mo**=month **NNT**=number needed to treat **NNH**=number needed to harm **NS**=non-statistically significant **SR**=sustained release (note we have used SR instead of SA in the trial write up given the potential for people to mis-interpret as short acting, as identified by reviewers.)

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References:

[1] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S. 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. JAMA. 2018 Mar 6;319(9):872-882. doi: 10.1001/jama.2018.0899. PubMed PMID: 29509867; PubMed. Central PMCID: PMC5885909. Supplemental content available at: https://jamanetwork.com/journals/jama/article-abstract/2673971?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2018.0899

[2] Supplemental content available at: https://jamanetwork.com/journals/jama/article-abstract/2673971?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2018.0899

[3] Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain — Part B: Recommendations for Practice, Version 5.5 April 30, 2010. [NOUGG] Accessed at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf