



Athens

5-7 October 2023

Placebo effect in Osteoarthritis: Why not use it to our advantage?

Gustavo Constantino de Campos

Departamento de Ortopedia - UNICAMP

Instituto Wilson Mello

 **drgustavoconstantino**



INSTITUTO WILSON MELLO

OA: ARE WE HAPPY WITH CURRENT TREATMENT?

- Guidelines don't agree on every treatment
- Literature is contradictory
- Most treatments have low Effect Size

Bannuru et al. OARSI Guideline. O&C 2019

Brophy et al. AAOS Guideline . JAAOS 2022

Kucharz et al. ESCEO Guideline. Rheumatol Int 2019

Kolasinski et al. ACR Guideline. Arth and Rheumatol 2019



IT'S EFFECT SIZE, STUPID!

- Effect Size takes standard deviation in account
- $ES = 1$: Mean at endpoint is 1 Standard Deviation higher than at baseline
- In practical terms:

$ES = 0,2$: small benefit

$ES = 0,5$: moderate benefit

$ES > 0,8$: major effect

Coe, Robert. "It's the effect size, stupid."
*British Educational Research Association
Annual Conference*. Vol. 12. 2002.

VISCOSUPPLEMENTATION EVIDENCE

COPYRIGHT © 2015 BY THE JOURNAL OF BONE AND JOINT SURGERY, INCORPORATED

Viscosupplementation for Osteoarthritis of the Knee

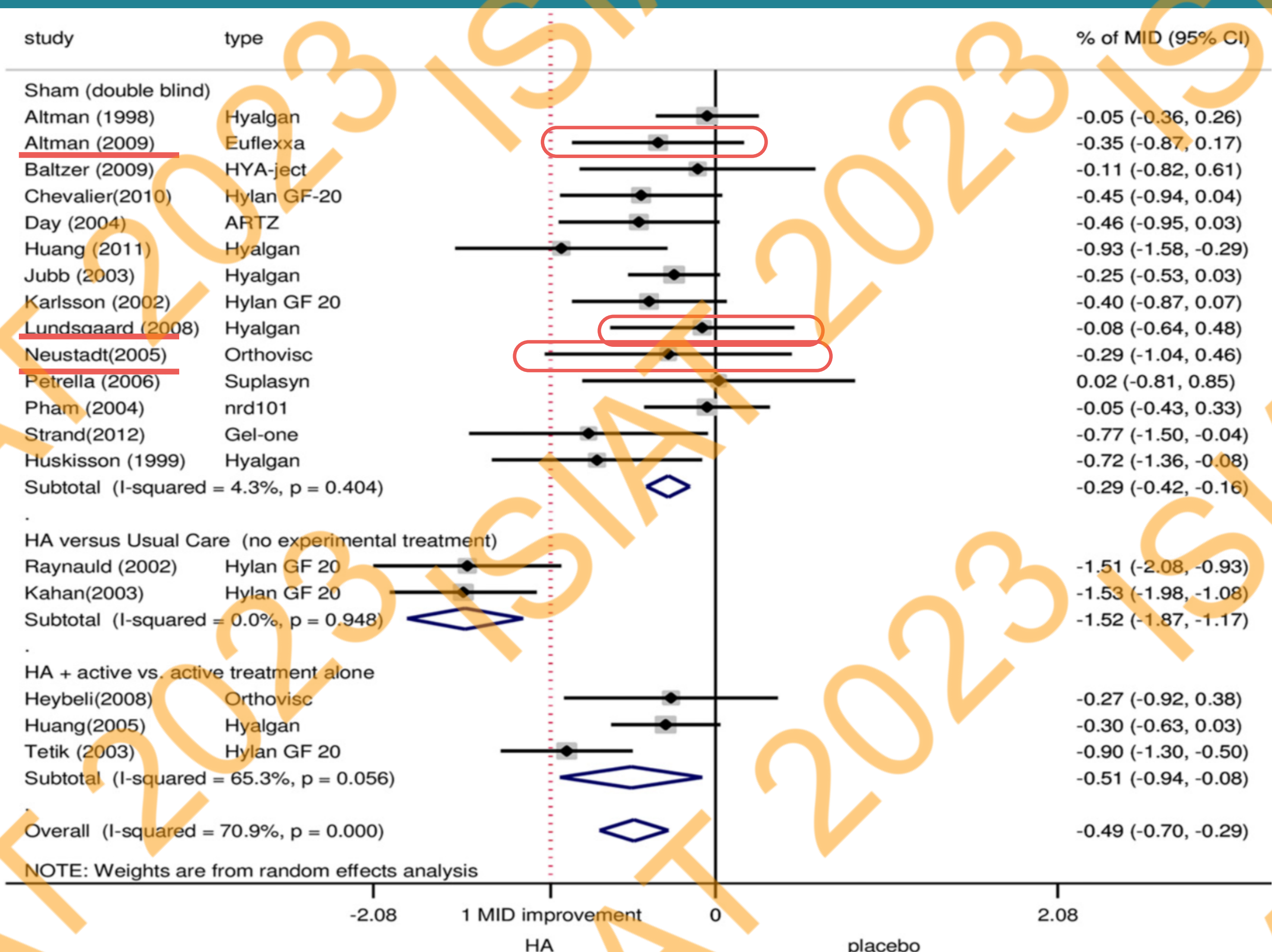
A Systematic Review of the Evidence

David Jevsevar, MD, MBA, Patrick Donnelly, MA, Gregory A. Brown, MD, PhD, and Deborah S. Cummins, PhD

Investigation performed at the American Academy of Orthopaedic Surgeons, Rosemont, Illinois

Conclusions: Meta-analysis of only the double-blinded, sham-controlled trials with at least sixty patients did not show clinically important differences of HA treatment over placebo.

VISCOSUPPLEMENTATION EVIDENCE

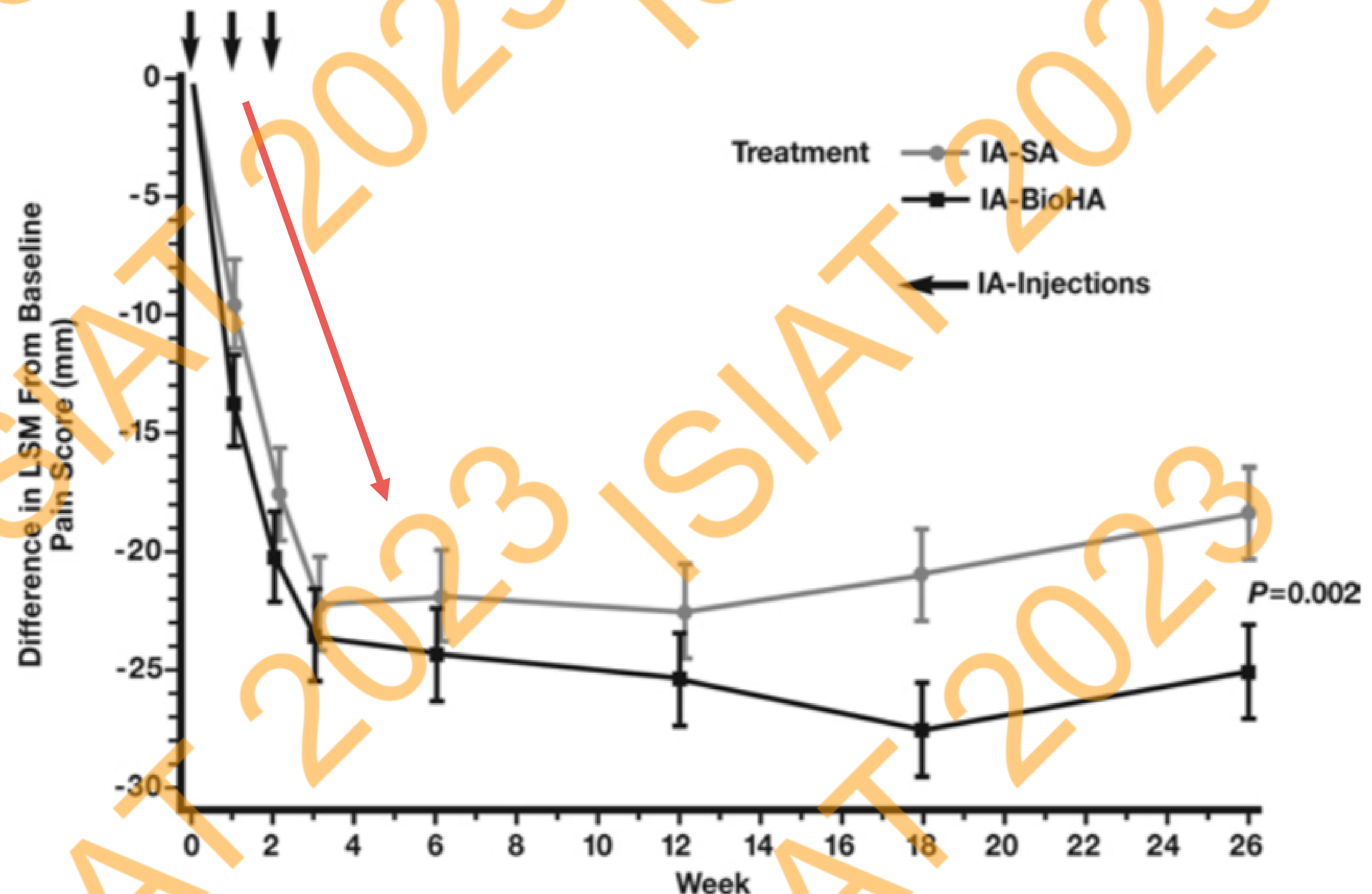


VISCOSUPPLEMENTATION EVIDENCE

A Double-Blind, Randomized, Saline-Controlled Study of the Efficacy and Safety of EUFLEXXA[®] for Treatment of Painful Osteoarthritis of the Knee, With an Open-Label Safety Extension (The FLEXX Trial)

Roy D. Altman, MD,* Jeffrey E. Rosen, MD,[†] Daniel A. Bloch, PhD,[‡]
Hind T. Hatoum, PhD,[§] and Paul Korner, MD, MBA[¶]

- Huge pain relief in both groups



VISCOSUPPLEMENTATION EVIDENCE

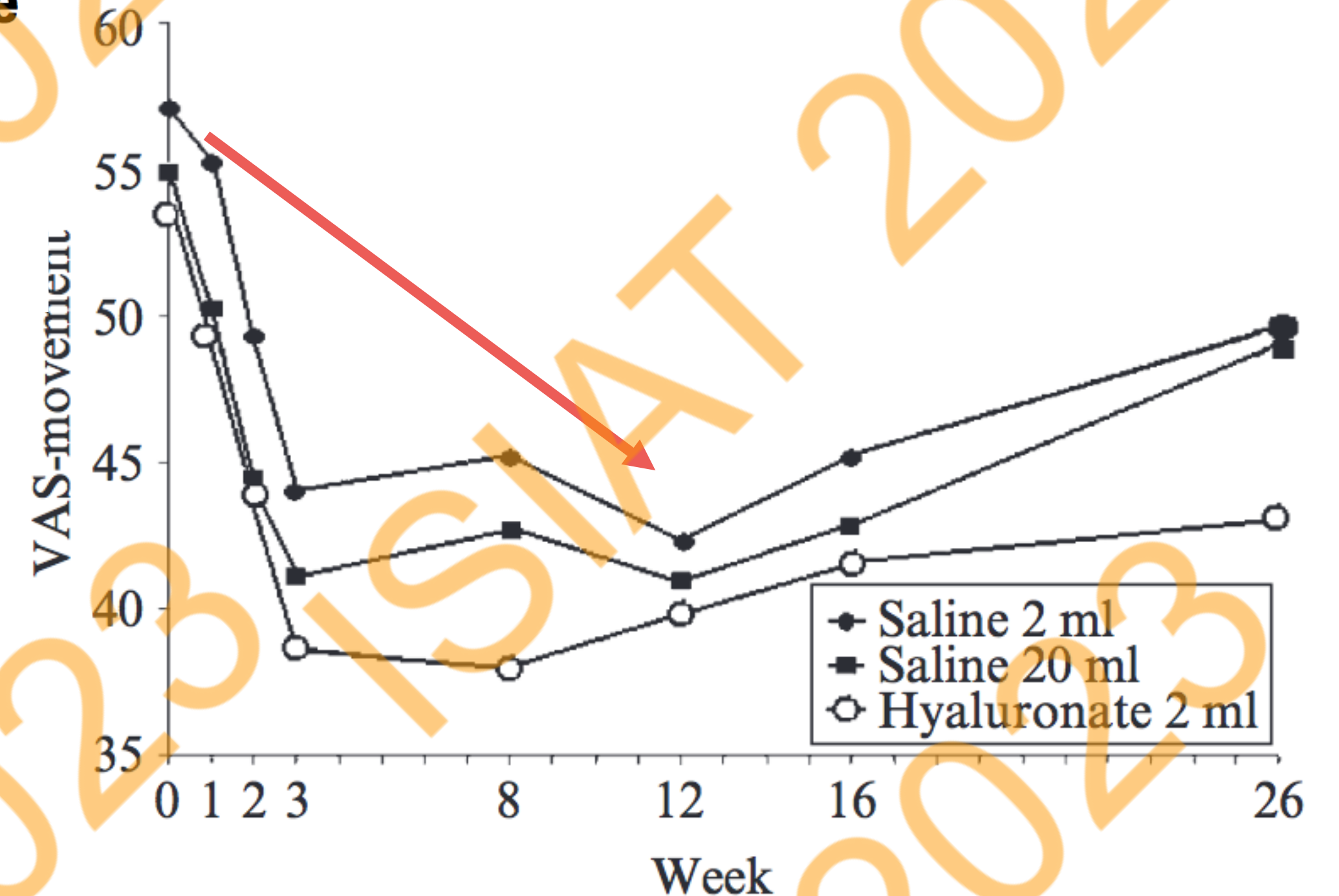
142

Scand J Rheumatol 2008;37:142–150

Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial

C Lundsgaard^{1,3}, N Dufour¹, E Fallentin², P Winkel³, C Gluud³

30% of improvement in all groups



Conclusions: Intra-articular hyaluronate or distention with physiological saline did not significantly reduce pain compared with physiological saline placebo in patients with osteoarthritis of the knee. (ClinicalTrials.gov number, NCT00144820)

VISCOSUPPLEMENTATION EVIDENCE

Clinical Effects of Intraarticular Injection of High Molecular Weight Hyaluronan (Orthovisc®) in Osteoarthritis of the Knee: A Randomized, Controlled, Multicenter Trial

DAVID NEUSTADT, JACQUES CALDWELL, MARY BELL, JOHN WADE, and JOSEPH GIMBEL

Huge improvement in all groups

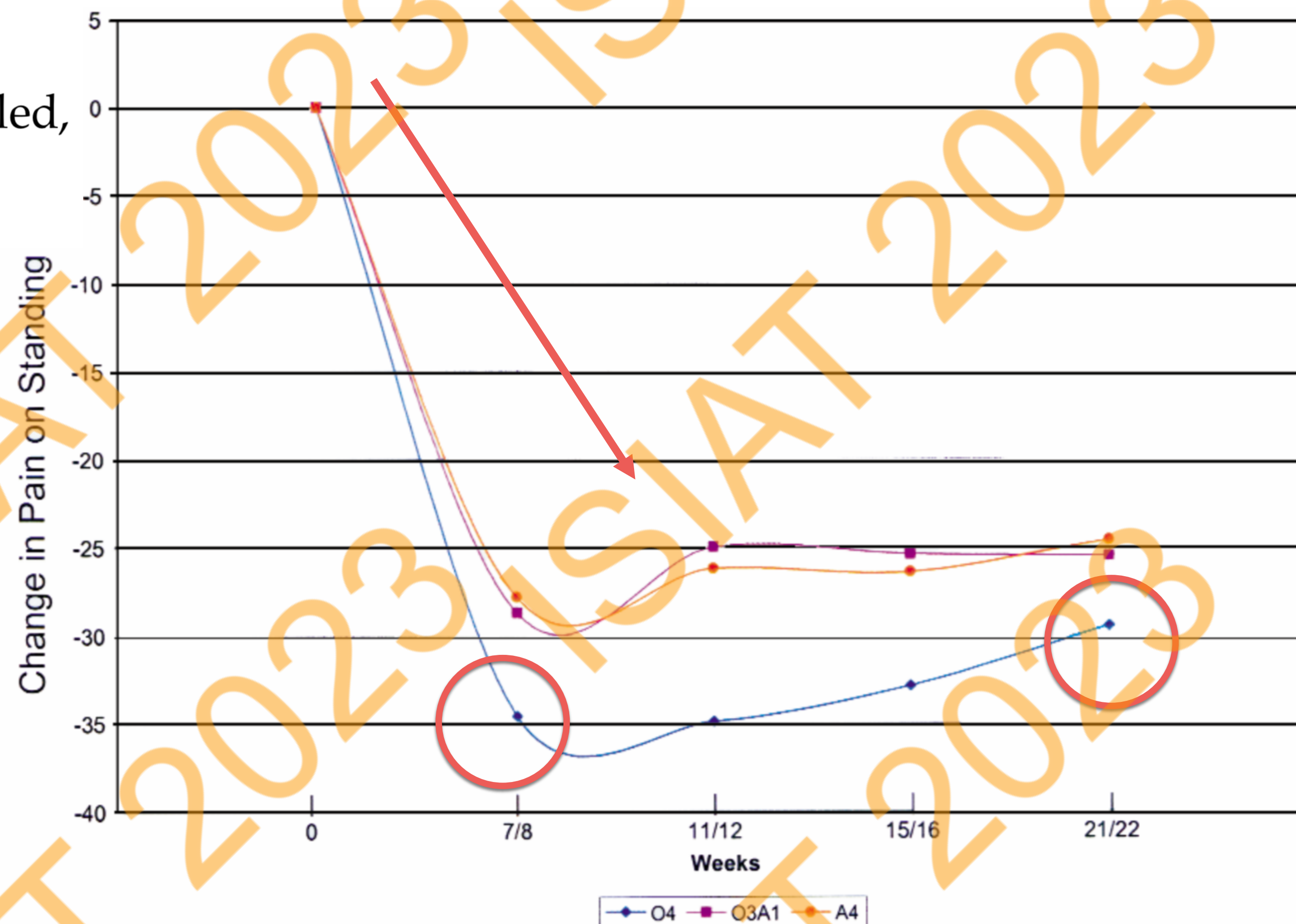


Figure 1. Mean change in Pain on Standing score. *Average baseline score: O4 = 64.8; O3A1 = 65.4; A4 = 65.9.

VISCOSUPPLEMENTATION EVIDENCE



EFFECT SIZE

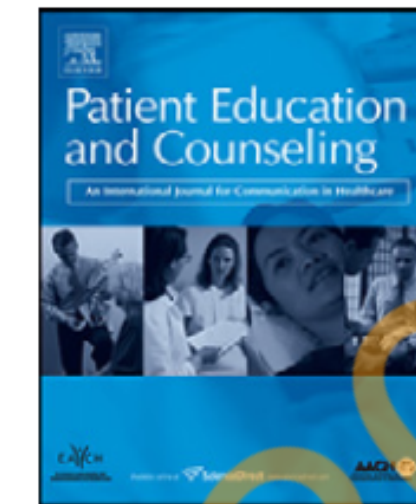


ELSEVIER

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou



Review

Self-management programs for chronic musculoskeletal pain conditions: A systematic review and meta-analysis

Shizheng Du^{a,b}, Changrong Yuan^{a,*}, Xian Xiao^b, Jing Chu^a, Yaoqin Qiu^a, Huijuan Qian^a

- ES=0,06 (0,02-0,1) for pain relief

Jansen et al: Exercise and manual therapy for knee osteoarthritis

Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review

Mariette J Jansen^{1,2}, Wolfgang Viechtbauer^{2,3}, Antoine F Lenssen^{4,5}, Erik JM Hendriks^{1,2} and Rob A de Bie^{1,2}

- Exercise: ES=0,34 for pain relief

REVIEW

Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis

Robin Christensen, Else Marie Bartels, Arne Astrup, Henning Bliddal

- Weight loss : ES=0,20 for pain; 0,23 for function

Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004257.

Acetaminophen for osteoarthritis.

Towheed TE¹, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G.

- ES=0,13 (pain)

Arthritis Rheum. 2005 Aug 15;53(4):510-8.

Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis.

Lee C¹, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ.

- ES=0,37 (pain)

Ann Intern Med. 2012 Aug 7;157(3):180-91. doi: 10.7326/0003-4819-157-3-201208070-00473.

Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis.

Rutjes AW¹, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S.

- ES=0.37 (pain)

Cochrane Database Syst Rev. ; (1): CD001977. doi:10.1002/14651858.CD001977.pub2.

Acupuncture for peripheral joint osteoarthritis

Eric Manheimer¹, Ke Cheng², Klaus Linde³, Lixing Lao⁴, Junghee Yoo⁵, Susan Wieland⁶, Daniëlle AWM van der Windt⁷, Brian M Berman¹, and Lex M Bouter⁸

- ES=0,28 for pain and function (vs “sham”)

Cochrane Database Syst Rev. ; (1): CD001977. doi:10.1002/14651858.CD001977.pub2.

Acupuncture for peripheral joint osteoarthritis

Eric Manheimer¹, Ke Cheng², Klaus Linde³, Lixing Lao⁴, Junghee Yoo⁵, Susan Wieland⁶, Daniëlle AWM van der Windt⁷, Brian M Berman¹, and Lex M Bouter⁸

- ES=0,28 for pain and function (vs “*sham*”)
- vs waiting list: ES=0.96 !!!

Clin Orthop Relat Res (2013) 471:613–620
DOI 10.1007/s11999-012-2659-y

Clinical Orthopaedics
and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

CLINICAL RESEARCH

Adding Triamcinolone Improves Viscosupplementation: A Randomized Clinical Trial

Gustavo Constantino de Campos MD,
Marcia U. Rezende MD, PhD, Alexandre F. Pailo MD,
Renato Frucchi MD, Olavo Pires Camargo MD, PhD

- Grupo VS (endpoint vs baseline): $ES=0,80$
- Grupo VS+T (endpoint vs baseline): **$ES=1,32$!!!!**

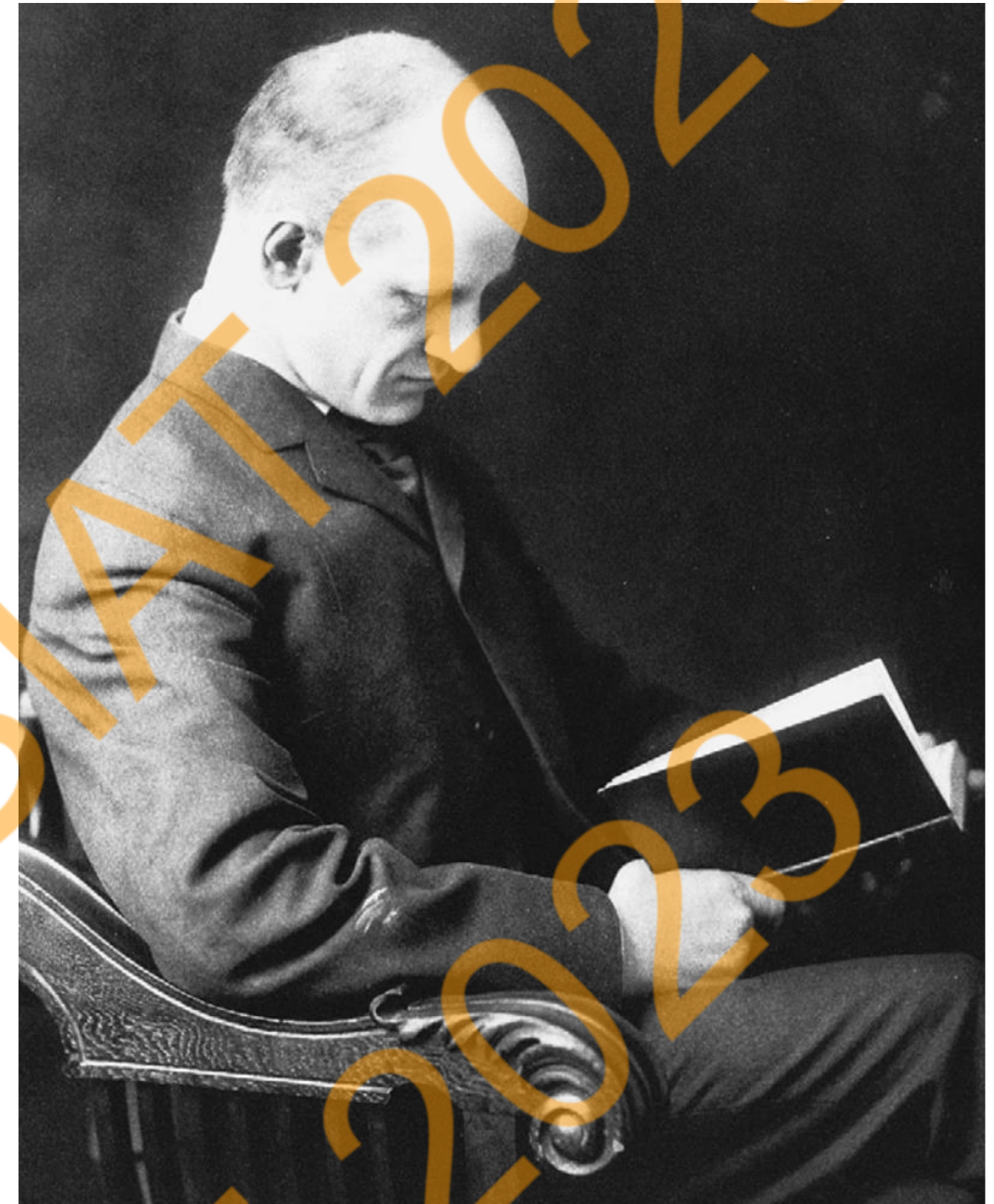
The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials

W Zhang,¹ J Robertson,¹ A C Jones,² P A Dieppe,³ M Doherty¹

- 198 trials in OA (193 vs placebo e 14 vs no treatment)
- placebo effect: difference between follow-up and baseline in the placebo group
- **ES=0,51 (placebo)** e 0,03 (no treatment)

PLACEBO

- Placebo: Latin for “I will please”
- XIII Century: Hired mourners chanted the 116 psalm
- Term “placebo” referred to “fake behavior”
- Until 1945: “Humble Humbug”



PLACEBO

- After WWII : RCTs - gold standart method
- Concept of: **POWERFUL PLACEBO** (Beecher)
- *“Total effect of a treatment: drug effect plus placebo effect”*
- Ethical consideration: Can we deceive our patients?
- Negative conotation

DEPARTMENT OF MEDICAL HISTORY

Department of medical history

Powerful placebo: the dark side of the randomised controlled trial

PLACEBO EFFECT

Symptomatic improvement that does not result from the substance or intervention itself

Placebo - UNETHICAL?



José Alencar
@josenalencar

O problema é que enquanto a população não souber

PEOPLE ARE BEING DECEIVED BY UNSCRUPULOUS
PROFESSIONALS

Dores serão enganadas por profissionais
inescrupulosos, mais gente acreditará em
pseudociência, mais longe da boa saúde estaremos.

PLACEBO EFFECT EVIDENCE

DEMONSTRATION TO MEDICAL STUDENTS OF PLACEBO RESPONSES AND NON-DRUG FACTORS

BARRY BLACKWELL SAUL S. BLOOMFIELD
C. RALPH BUNCHER

*College of Medicine, University of Cincinnati,
Cincinnati, Ohio 45229, U.S.A.*

THE LANCET, JUNE 10, 1972

- Students received 1 or 2 pills, blue or pink
- 2 pills produced more effects than one
- Blues were more sedative

PLACEBO EFFECT EVIDENCE

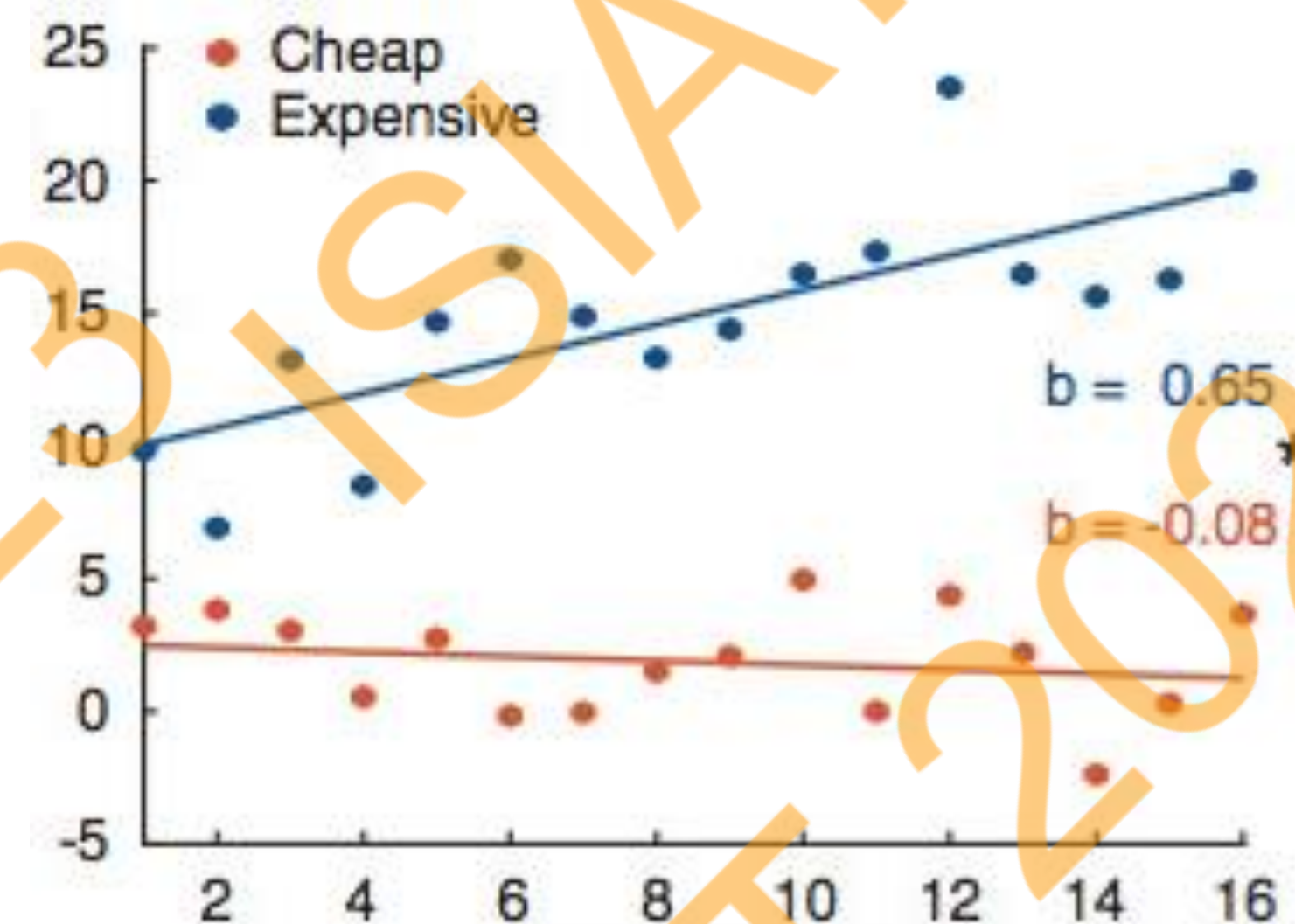
JAMA. 2008 Mar 5;299(9):1016-7. doi: 10.1001/jama.299.9.1016.

Commercial features of placebo and therapeutic efficacy.

Waber RL, Shiv B, Carmon Z, Ariely D.

Better results when:

- Show the brand
- It is more expensive



Double-blind versus deceptive administration of a placebo

I Kirsch¹, L J Weixel

Subjects were give decaffeinated coffee

- Group 1: Led to believe it was coffee
- Group 2: Led to believe it was a RCT

THE LANCET



Volume 325, Issue 8419, 5 January 1985, Page 43

Letters to the Editor

CLINICIANS' EXPECTATIONS INFLUENCE PLACEBO ANALGESIA

Richard H. Gracely, Ronald Dubner, William R. Deeter, Patricia J. Wolskee

Placebo vs Nocebo

How to combat nocebo effects

Talk to other people



What does the doctor say?



Inform yourself



How does the doctor say it?



A Randomized Controlled Trial of Acupuncture for Osteoarthritis of the Knee: Effects of Patient-Provider Communication

Maria E. Suarez-Almazor, M.D., Ph.D., Carol Looney, M.S., C.H.E.S., YanFang Liu, M.D.,

- ACP vs sham: no difference
- Difference in style of caregiver

Arthritis Rheum. 1989 Dec;32(12):1577-83.

Can the provision of information to patients with osteoarthritis improve functional status? A randomized, controlled trial.

Weinberger M¹, Tierney WM, Booher P, Katz BP.

- Patients received phonecalls



REVIEW

Annals of Internal Medicine

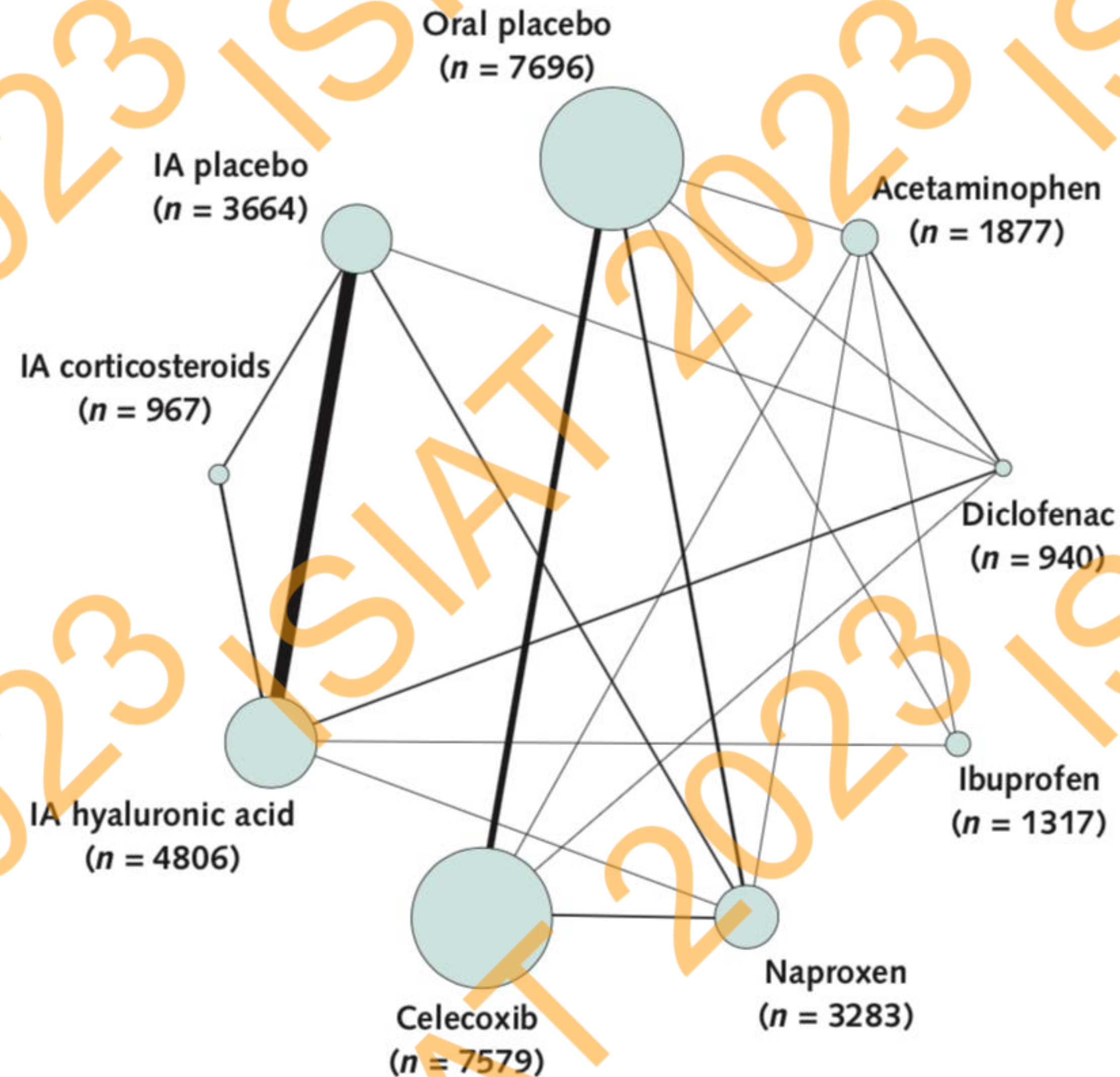
Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis

A Systematic Review and Network Meta-analysis

Raveendhara R. Bannuru, MD; Christopher H. Schmid, PhD; David M. Kent, MD; Elizaveta E. Vaysbrot, MD; John B. Wong, MD; and Timothy E. McAlindon, MD

- Network analysis estimates relative effects of all treatments against each other
- 137 studies - 33243 patients
- Treatments: IA corticoids, VS, acetaminofen, NSAIDs, IA placebo, oral placebo

PLACEBO EVIDENCE



PLACEBO EVIDENCE

Comparator

Effect Sizes (95% CrI), by Treatment

	Acetaminophen	IA Placebo	Celecoxib	Naproxen
Oral placebo	0.18 (0.04 to 0.33)†	0.29 (0.04 to 0.54)†	0.33 (0.25 to 0.42)†	0.38 (0.27 to 0.49)†
Acetaminophen	-	0.11 (-0.17 to 0.38)	0.15 (0.00 to 0.30)	0.20 (0.03 to 0.37)†
IA placebo	-	-	0.04 (-0.21 to 0.30)	0.09 (-0.15 to 0.34)
Celecoxib	-	-	-	0.05 (-0.08 to 0.17)
Naproxen	-	-	-	-
Ibuprofen	-	-	-	-
Diclofenac	-	-	-	-
IA corticosteroids	-	-	-	-

	Diclofenac	IA Corticosteroids	IA Hyaluronic Acid
Oral placebo	0.52 (0.34 to 0.69)†	0.61 (0.32 to 0.89)†	0.63 (0.39 to 0.88)†
Acetaminophen	0.33 (0.12 to 0.54)†	0.42 (0.12 to 0.73)†	0.45 (0.18 to 0.72)†
IA placebo	0.23 (-0.03 to 0.49)	0.32 (0.16 to 0.47)†	0.34 (0.26 to 0.42)†
Celecoxib	0.18 (-0.01 to 0.37)	0.27 (-0.02 to 0.56)	0.30 (0.04 to 0.55)†
Naproxen	0.13 (-0.07 to 0.33)	0.22 (-0.06 to 0.51)	0.25 (0.01 to 0.49)†
Ibuprofen	0.07 (-0.17 to 0.32)	0.16 (-0.15 to 0.48)	0.19 (-0.09 to 0.47)
Diclofenac	-	0.09 (-0.20 to 0.38)	0.11 (-0.14 to 0.37)
IA corticosteroids	-	-	0.02 (-0.12 to 0.17)

TAKE HOME MESSAGE



ISIAT 2023

TAKE HOME MESSAGE

- Placebo effect is powerfull, specially in OA

TAKE HOME MESSAGE

- Placebo effect is powerfull, specially in OA
- Your behavior and what you say can be more important than the drug itself

TAKE HOME MESSAGE

- Placebo effect is powerfull, specially in OA
- Your behavior and what you say can be more important than the drug itself
- Patient expectation and caregiver expectation influences results

TAKE HOME MESSAGE

- Placebo effect is powerfull, specially in OA
- Your behavior and what you say can be more important than the drug itself
- Patient expectation and caregiver expectation influences results
- The more invasive higher the placebo effect

CONCLUSION

Placebo effect is ***REAL and POWERFULL***

We should and **MUST** use it to help our patients



THANK YOU

EDITORIAL

Placebo effect in osteoarthritis: Why not use it to our advantage?

Gustavo C de Campos

W J O World Journal of
Orthopedics

