Treatment	Differential Placebo Effect		Single Placebo Effect	
	Effect Size (95% CrI)	Rank	Effect Size (95% CrI)	Rank
Reference	Oral Placebo	NA	All Placebos combined into a single effect	NA
IA Hyaluronic acid	0.60 (0.40, 0.80)	1	0.34 (0.27, 0.42)	2
IA Corticosteroids	0.58 (0.34, 0.82)	2	0.32 (0.17, 0.47)	3
Non-selective NSAIDs	0.43 (0.35, 0.51)	3	0.37 (0.29, 0.44)	1
Topical NSAIDs	0.34 (0.19, 0.49)	4	0.21 (0.10, 0.32)	5
Cox-2 selective NSAIDs	0.34 (0.27, 0.41)	5	0.31 (0.24, 0.39)	4
Acetaminophen	0.18 (0.05, 0.30)	6	0.15 (0.02, 0.28)	6

Figure 3. Standardized mean differences of active treatments for pain at 12 weeks comparing results from deferential placebo effect network and single placebo effect network

Results: We identified 140 studies including 37,908 participants with an age range of 45 - 75 years. The proportion of women ranged from 28% - 100%. For pain, IA placebo (SMD, 95% Credible Interval) [0.28 (0.08, 0.48)] and topical placebo [0.20 (0.02, 0.38)] had significantly greater effects than oral placebo. The relative efficacies and the hierarchy of the active treatments were substantially changed by ignoring the differential response to the placebo types (Figures 2 & 3). For example, in the differential placebo network model, IA and topical therapies rank higher than oral, while in the non-differential placebo network model, oral NSAIDs ranked higher.
Conclusions: Our results show that some types of placebo interventions are associated with greater responses. This supports the notion that some placebo treatments can exert clinically relevant effects. In other words, the method of treatment delivery might have an important influence on outcome. These important differences also need to be accounted for in the design of future OA studies.

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RANDOMIZED, DOUBLE-BLIND, MULTICENTER, NON INFERIORITY CLINICAL TRIAL WITH COMBINED GLUCOSAMINE AND CHONDROITIN SULFATE VS CELECOXIB FOR PAINFUL KNEE OSTEOARTHRITIS

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Purpose: The fixed dose combination of glucosamine hydrochloride and chondroitin sulfate (2 capsules GHcl+CS; 250 mg and 200 mg, respectively, three times daily) was found to be efficacious compared to placebo in subjects with knee osteoarthritis (OA) with severe pain in the NIH-funded Glucosamine Arthritis Intervention Trial (GAIT) (N Engl J Med 2006 Feb 23;354(8):795-808). The proportion of OA patients who achieved the primary endpoint of a 20% improvement in pain was similar between those randomized to GHcl+CS and celecoxib 200 mg daily in this 6-month symptom study. Subsequently, a phase IV randomized controlled non-inferiority trial was designed to compare the efficacy of GHcl+CS and celecoxib in patients with knee OA to extend the findings from GAIT.
Methods: The Multicentric Osteoarthritis interVEntion Study with Sysadoa (MOVES) was designed as a non-inferiority trial to compare the efficacy and safety of a fixed dose combination of GHcl+CS (Droglican, Bioiberica SA, Barcelona, Spain) and celecoxib in patients with symptomatic knee OA with severe pain. Patients were randomized in a double-blind, double-dummy fashion to receive either 2 capsules of Droglican (GHcl 250 mg and CS 200 mg) three times daily, or Celecoxib 200 mg capsule plus 5 placebo Droglican capsules per day. Patients were eligible if they were aged 40 and above, fulfilled American College of Rheumatology criteria for knee OA, had Kellgren-Lawrence (KL) grade 2 or 3 radiographic severity and had a WOMAC pain scale of >301 units (0-500 scale). Patients with high gastrointestinal or cardiovascular risk were excluded. The primary outcome was the mean decrease in WOMAC Pain subscale after 6 months of treatment; the non-inferiority margin was set at 40 (corresponding to 8 mm on a 0-100 mm scale) and the sample size was calculated at 240 per group with 90% power. Mixed model repeated measures was used to analyse the primary outcome; time, treatment and time x treatment were included as fixed effects.
Results: A total of 763 patients were screened and 606 randomized to receive either Droglican (N=304) or celecoxib (N=302). Of these, 522 (86.1%) completed the 6-month trial and were included in the per-protocol non-inferiority analysis; there was no difference in proportion completing between groups. Mean (SD) age was 62.7 (8.9) years, 438 (83.9%) were women; KL grade 2 changes were present in 327 (62.6%). The mean (SD) WOMAC pain score at randomization was 372.0 (41.8) and 370.6 (41.4) in the Droglican and celecoxib groups, respectively. The mean (SD) WOMAC pain score at 180 days was 185.8 (7.4) and 184.7 (7.6) in the Droglican and celecoxib groups, respectively, corresponding to a mean (SEM) difference of 1.11 (10.63) units (95% confidence interval -21.99, 19.76) (P = 0.917) that respects the non-inferiority margin. These results were robust in sensitivity analyses using the intention-to-treat population and when baseline observation carried forward was used for imputation in both the per-protocol and intent-to-treat populations. In addition, there was no significant difference between the Droglican and celecoxib groups in the absolute improvement in the WOMAC stiffness and function scales and the five individual items of the WOMAC pain scale at 6 months. There was no significant difference in the proportion of patients with treatment-emergent adverse events between the groups (50.7% overall); no deaths occurred in this 6-month study.
Conclusions: These results demonstrated comparable efficacy of a fixed dose combination of glucosamine hydrochloride and chondroitin sulphate (Droglican) to celecoxib for relief of severe knee pain in patients with knee OA and a similar safety profile. Further ongoing analyses will examine key secondary endpoints including responder indices in this population.

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STUDY OF THE EFFECT OF CHONDROITIN SULFATE ON PAIN IN KNEE OSTEOARTHRITIS PATIENTS ASSESSED BY FUNCTIONAL MRI: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

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Purpose: The aim of the present fMRI study was to objectively identify the effects of Chondroitin Sulfate (CS) treatment on the brain response to pressure painful stimulation in patients with radiological and clinical knee osteoarthritis.
Material and methods: The current study was developed in the Rheumatology Department and the MRI Research Unit of the Hospital del Mar in Barcelona, from December 2010 to January 2013. This is a phase IV, randomized, double-blind clinical trial in which patients received CS (Condrosan®, Bioibérica S.A.) 800 mg/day or placebo for a 4-month treatment course. 64 patients were randomized (32 to placebo and 32 to CS), and finally 51 patients were evaluable by ITT (27 in the placebo group and 24 in the CS group). Patients were assessed at baseline and post-treatment. Two tests were conducted in each session by applying painful pressure on the patella surface and on the knee medial interline, using a MRI-compatible algometer, during the acquisition of two 6-min fMRI sequences. Stimulus intensity to be applied in both fMRI sessions was individually adjusted prior to baseline fMRI. Each subject was asked to rate the subjective pain perceived during the whole fMRI sequence immediately after fMRI acquisition using NRS. All fMRI data were processed using the Statistical Parametric Mapping (SPM8) package, Wellcome Department of Imaging Neuroscience, running in Matlab