

Which Meta-Analyses Should I Trust?

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Outline

- Outcomes
- Synthesis
- Heterogeneity between trials
- Trial methodology
- Trial size
- Example: chondroitin sulfate

#1: Outcomes



EDITORIALS

Knee Pain Is the Malady – Not Osteoarthritis

Osteoarthritis is a well-defined pathoanatomic entity readily demonstrable by modern imaging techniques. For a century, the pathology that is this disease has been ingrained in the mind of every medical student.

598 1 April 1992 • *Annals of Internal Medicine* • Volume 116 • Number 7

Hadler, *Ann Intern Med* 1992

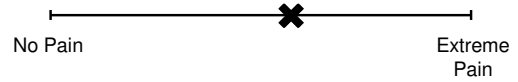
#2: Synthesis

Pain-related outcomes

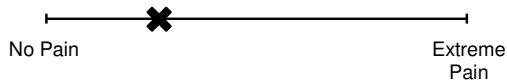
1. Global pain score
2. Pain on walking
3. WOMAC osteoarthritis index pain subscore
4. Composite pain scores other than WOMAC
5. Pain on activities other than walking
6. WOMAC global score
7. Lequesne osteoarthritis index global score
8. Other algofunctional composite scores
9. Patient's global assessment
10. Physician's global assessment

Jüni et al, Best Pract Res Clin Rheumatol 2006

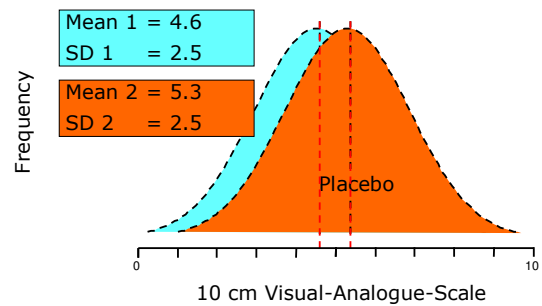
10 cm Visual Analogue Scale Time point: 0 days



10 cm Visual Analogue Scale Time point: 180 days



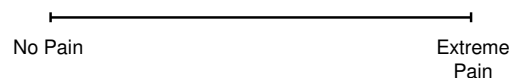
Distribution of raw data



Ingredients required for meta-analysis

- Measure of treatment effect: m
- Number of patients: n
- Measure of variability: SD

Rule of thumb: 4 SDs cover the range of plausible values



Standardised weighted mean difference = effect size

$$\frac{\text{Difference in pain scores}}{\text{Pooled standard deviation}}$$

Typical standard deviations

- 10 cm Pain Visual Analogue Scale (range 0-10)
 - Standard deviation ~ 2.5
- WOMAC pain subscale (range 0-20)
 - Standard deviation ~ 5

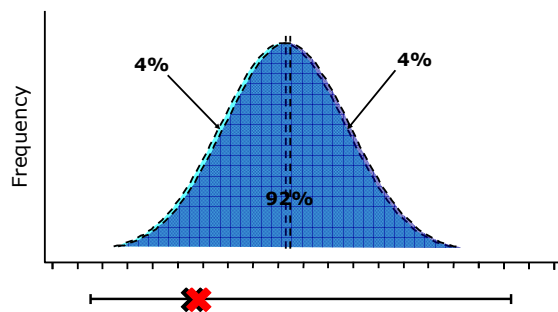
Pooled standard deviation

$$SD_{pooled} = \sqrt{\frac{SD_{Exp}^2 + SD_{Con}^2}{2}}$$

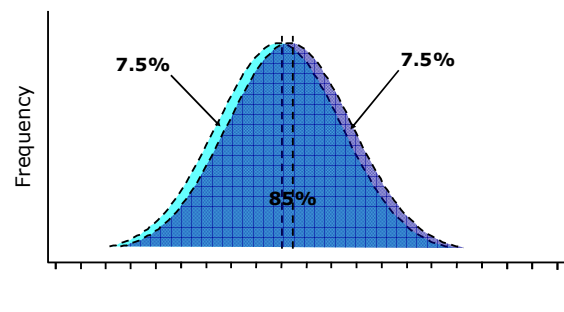
Magnitude of effect	Effect size	Approximate corresponding mean differences in scores between experimental and control groups	
		WOMAC pain subscale (0 to 20)	Pain 10 cm visual analogue scale (0 to 10)
Small	-0.10	-0.4	-0.25
	-0.20	-0.8	-0.50
	-0.30	-1.2	-0.75
Medium	-0.40	-1.6	-1.00
	-0.50	-2.0	-1.25
	-0.60	-2.4	-1.50
Large	-0.70	-2.8	-1.75
	-0.80	-3.2	-2.00
	-0.90	-3.6	-2.25
	-1.00	-4.0	-2.50

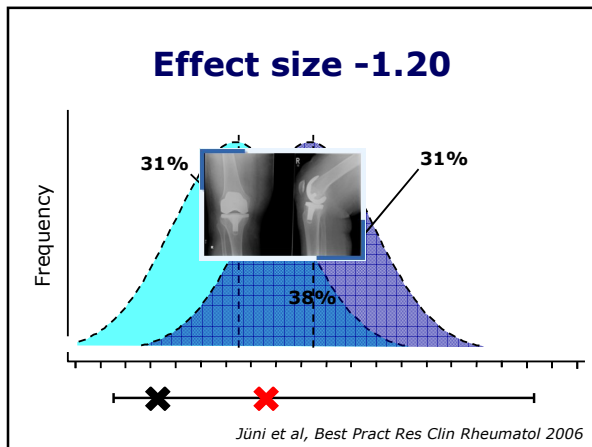
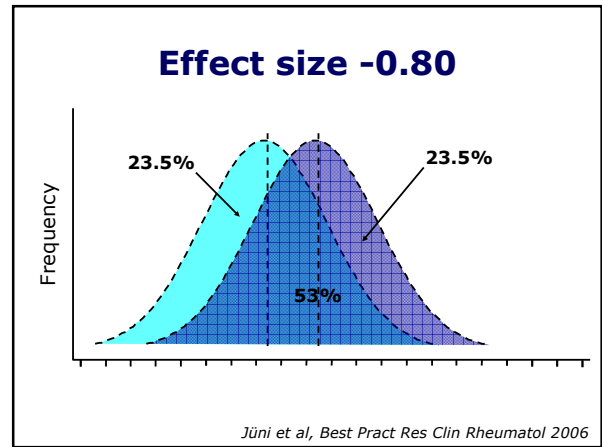
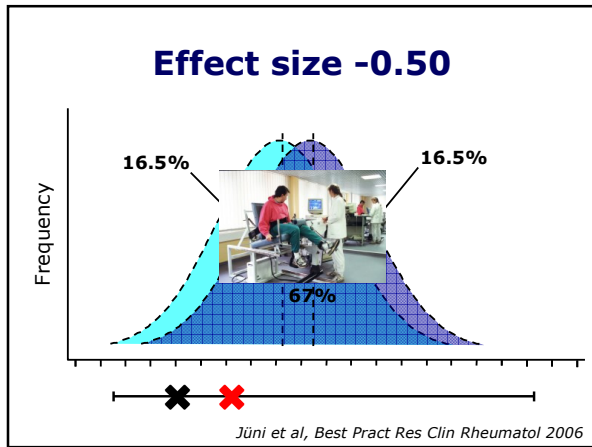
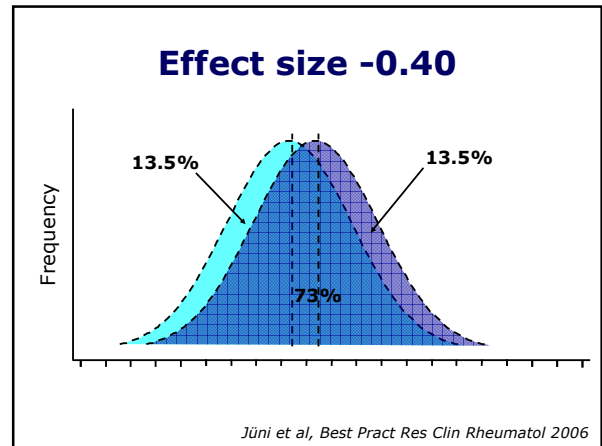
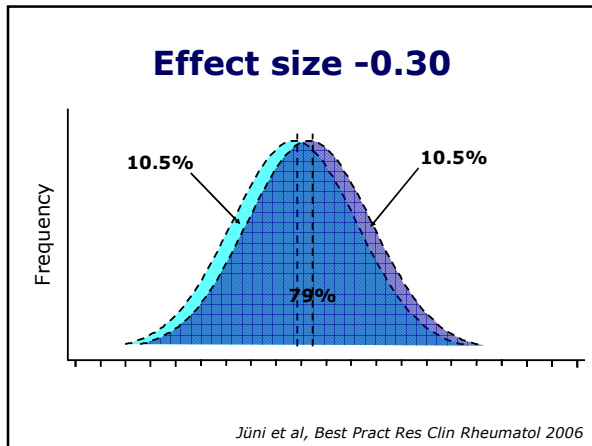
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.10



Effect size -0.20





#3: Heterogeneity



Meta-analysis: Chondroitin for Osteoarthritis of the Knee or Hip

Stephan Reichenbach, MD; Rebekka Sterchi, MD; Martin Scherer, MD; Sven Trelle, MD; Elizabeth Bürzi, PhD; Ulrich Bärzi, MD; Paul A. Dieppe, MD; and Peter Jüni, MD

Background: Previous meta-analyses described moderate to large benefits of chondroitin in patients with osteoarthritis. However, recent large-scale trials did not find evidence of an effect.

Purpose: To determine the effects of chondroitin on pain in patients with osteoarthritis.

Data Sources: The authors searched the Cochrane Central Register of Controlled Trials (1970 to 2006), MEDLINE (1966 to 2006), EMBASE (1980 to 2006), CINAHL (1970 to 2006), and conference proceedings; checked reference lists; and contacted authors. The last update of searches was performed on 30 November 2006.

Study Selection: Studies were included if they were randomized or quasi-randomized, controlled trials that compared chondroitin with placebo or with no treatment in patients with osteoarthritis of the knee or hip. There were no language restrictions.

Data Extraction: The authors extracted data in duplicate. Effect sizes were calculated from the differences in means of pain-related outcomes between treatment and control groups at the end of the trial, divided by the pooled SD. Trials were combined by using random-effects meta-analysis.

Data Synthesis: 20 trials (3846 patients) contributed to the meta-analysis, which revealed a high degree of heterogeneity among the

trials ($I^2 = 92\%$). Small trials, trials with unclear concealment of allocation, and trials that were not analyzed according to the intention-to-treat principle showed larger effects in favor of chondroitin than did the remaining trials. When the authors restricted the analysis to the 3 trials with large sample sizes and an intention-to-treat analysis, 40% of patients were included. This resulted in an effect size of -0.03 (95% CI, -0.13 to 0.07 ; $P = 0.5$) and corresponded to a difference of 0.6 mm on a 10-cm visual analogue scale. A meta-analysis of 12 trials showed a pooled relative risk of 0.99 (CI, 0.76 to 1.31) for any adverse event.

Limitations: For 9 trials, the authors had to use approximations to calculate effect sizes. Trial quality was generally low, heterogeneity among the trials made initial interpretation of results difficult, and exploring sources of heterogeneity in meta-regression and stratified analyses may be unreliable.

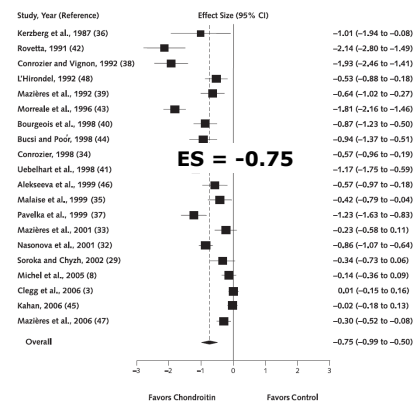
Conclusions: Large-scale, methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or non-existent. Use of chondroitin in routine clinical practice should therefore be discouraged.

Ann Intern Med. 2007;146:580-590.
For author affiliations, see end of text.

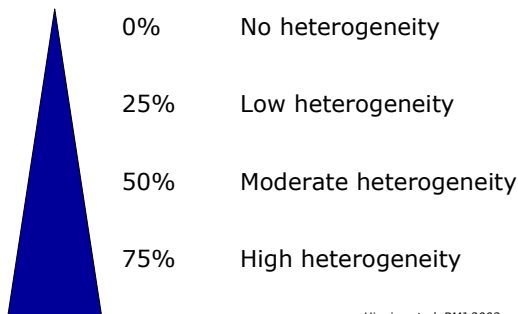
www.annals.org

Results

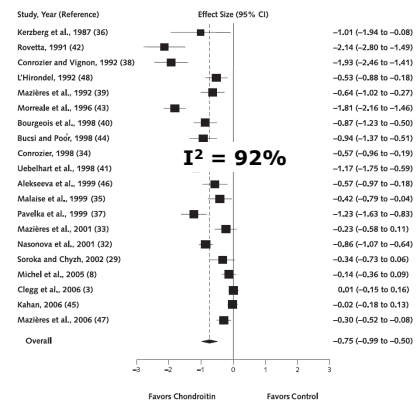
- 20 trials
- 3846 patients

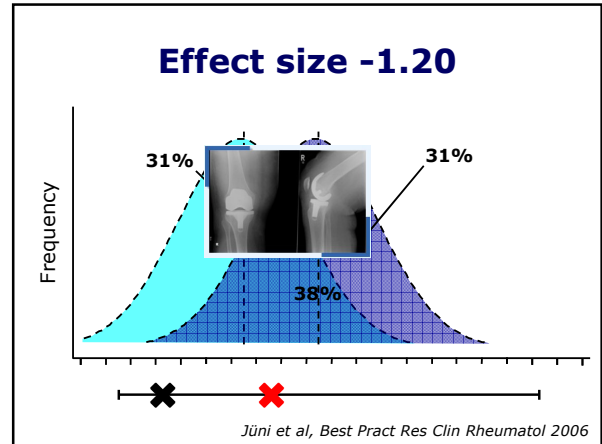
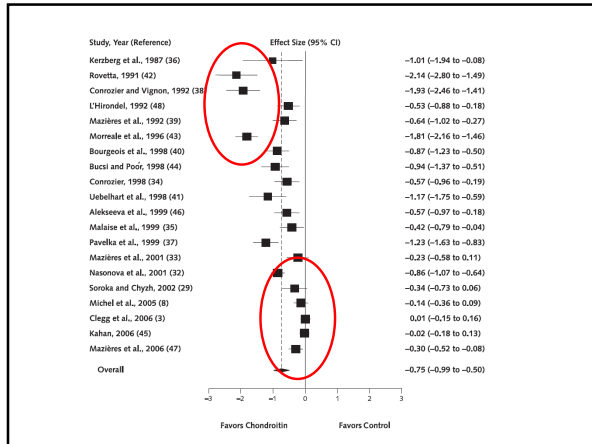


Heterogeneity: I² Statistic



Higgins et al, BMJ 2003





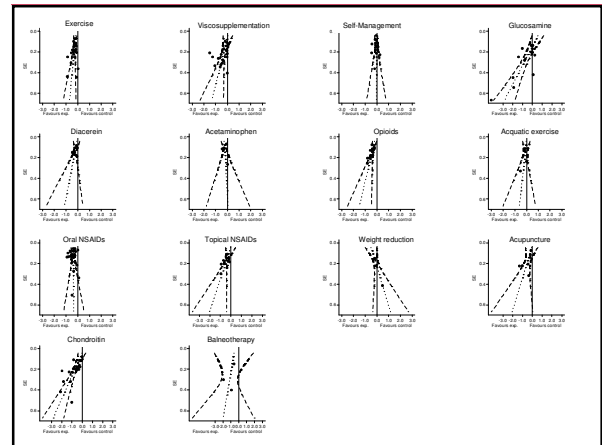
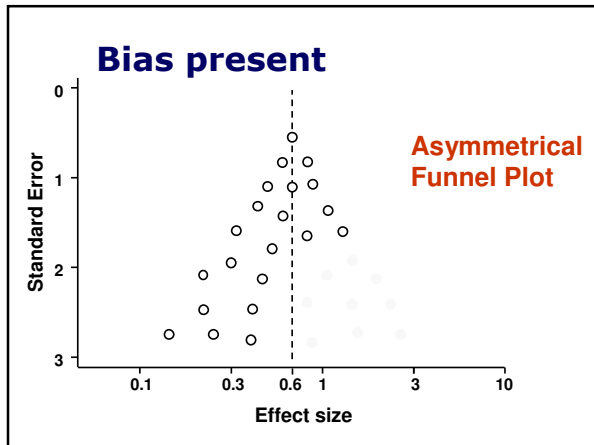
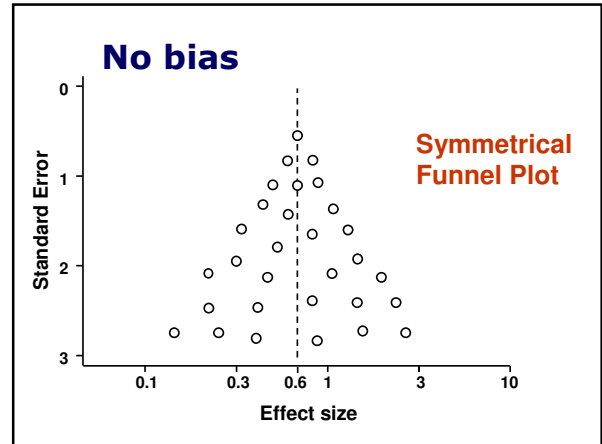
#4: Trial methodology

Variable	Total Trials, n	Patients Who Were Randomly Assigned, n	Effect size (95% CI)	I ² , %	P Value for Interaction
Concealment of allocation					
Adequate			-0.01 (-0.12 to 0.10)	0	0.050
Unclear			-0.84 (-1.08 to -0.59)		
Patient blinding					
Adequate	12	1952	-0.93 (-1.34 to -0.51)	95	0.22
Unclear or no	8	1894	-0.53 (-0.81 to -0.24)	86	
Intention-to-treat analysis					
Yes	3	1553	-0.03 (-0.13 to 0.07)	0	0.017
No or unclear	17	2293	-0.88 (-1.13 to -0.64)	86	
Patients randomly assigned					
>200 patients	5	2419	-0.26 (-0.56 to 0.04)	92	0.022
≤200 patients	15	1427	-0.93 (-1.22 to -0.65)	86	
Duration of follow-up					
>6 mo	11	2430	-0.55 (-0.81 to -0.29)	88	0.152
≤6 mo	9	1416	-0.98 (-1.49 to -0.48)	95	
Funding by nonprofit organization					
Yes	1	631	0.01 (-0.15 to 0.16)	-	0.186
Unclear or no	19	3215	-0.79 (-1.04 to -0.54)	91	
Route of administration					
Oral	18	3789	-0.67 (-0.92 to -0.43)	92	0.062
Intramuscular	2	57	-1.63 (-2.73 to -0.53)	74	
Analgesic co-intervention					
Similar	5	1929	-0.30 (-0.62 to 0.02)	91	0.043
Less in experimental group or unclear	15	1917	-0.92 (-1.26 to -0.59)	92	

Variable	Total Trials, n	Patients Who Were Randomly Assigned, n	Effect Size (95% CI)	I ² , %	P Value for Interaction
All trials	20	3846	-0.75 (-0.99 to -0.50)	92	-
Concealment of allocation					
Adequate	2	1253	-0.01 (-0.12 to 0.10)	0	0.050
Unclear	18	2593	-0.84 (-1.08 to -0.59)	88	
Placebo control					
Yes	17	3091	-0.78 (-1.06 to -0.50)	93	0.63
No	3	755	-0.62 (-0.94 to -0.30)	65	
Intention-to-treat analysis					
Yes			-0.03 (-0.13 to 0.07)	0	0.017
No or unclear			-0.88 (-1.13 to -0.64)	86	
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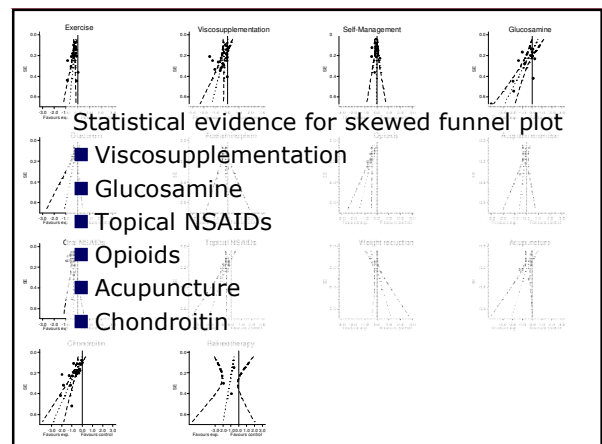
#5: Trial size

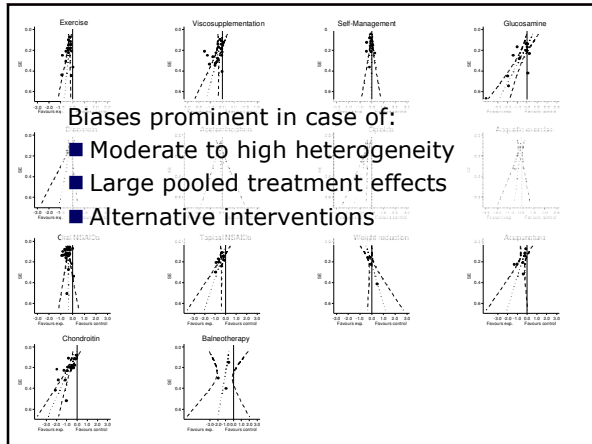
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Concomitant of allocation					0.050
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Unclear	18	2593	-0.84 (-1.08 to -0.59)	88	
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Yes	17	3091	-0.78 (-1.06 to -0.50)	93	
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Adequate	12	1952	-0.93 (-1.34 to -0.51)	95	
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Patients randomly assigned					
>200 patients			-0.26 (-0.56 to 0.04)	0	0.022
≤200 patients			-0.93 (-1.22 to -0.65)		
≤6 mo	9	1416	-0.98 (-1.49 to -0.48)	95	
Funding by nonprofit organization					0.186
Yes	1	631	0.01 (-0.15 to 0.16)	-	
Unclear or no	19	3215	-0.79 (-1.04 to -0.54)	91	
Route of administration					0.062
Oral	18	3789	-0.67 (-0.92 to -0.43)	92	
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Trial size

- May be the best single proxy for likelihood of bias





Which Meta-Analyses Should I Trust?

- Outcomes relevant for patients
- True synthesis of evidence using effect sizes
- Several large trials of ≥ 200 patients
- Concealed allocation
- ITT analysis
- Patient blinding if feasible
- Little heterogeneity between trials

