

## Is best available evidence the best?



Rome, September 18<sup>th</sup> 2008  
Presentation at pre-congress workshop

TREATMENT GUIDELINES  
FOR OSTEOARTHRITIS:  
DO THEY HELP AND CAN  
THEY BE IMPROVED?

Jan M. Bjordal  
Professor, PT, PhD,

Bergen University College of University of Bergen, Norway



No potential conflict of interest relationships exist with regard to my presentation.

## Which one to pick, consensus or meta-analyses results?

Meta-analyses Consensus



A compromise



A consensus-oriented approach



A "hard data"-oriented approach

## Consensus or meta-analyses?

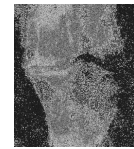
1. Should researchers restrict themselves to provide evidence in terms of trials, systematic reviews and meta-analyses?
2. Should researchers get involved in the making of guidelines?
3. Isn't consensus about politics in professional or health issues, not science?
4. If you go for consensus, what do you need science for?
5. Is it healthy for science pluralism that reviewers and editors participate in the making of guidelines, or may we end up with a consensus monopoly of opinions with a pseudo-scientific alibi?



## Meta-analyses as evidence

- Meta-analyses can be useful across interventions in areas where multiple therapies exist.
- The validity of using meta-analyses for comparisons rests on similarities in:

1. Patient samples,
2. Outcome measures,
3. Timing of outcome measurements,
4. Assessment of side-effects (tends to be qualitative)



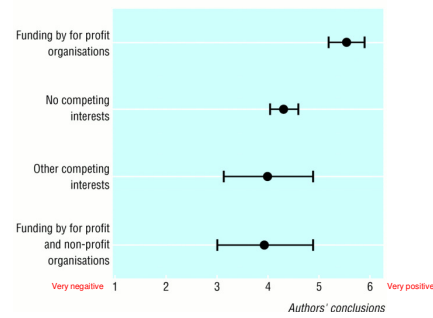
## Problems with consensus-based guidelines

Open to stakeholder bias, hidden agendas, etc.



DailyMirror, UK, Jan 6th, 2003

## Relationship between funding and trial conclusions



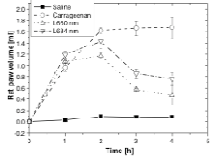
Kjaergard, L. L. et al. BMJ 2002;325:249



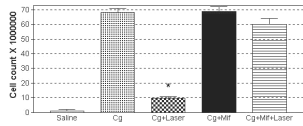


## Laser in inflammation

### Animal studies



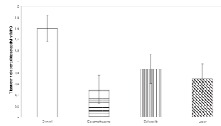
Anti-inflammatory effect of laser is non-wavelength specific  
Albertini, Bjordal et al. 2008  
Photomed Laser Surg



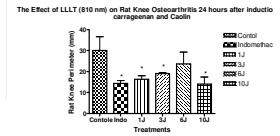
Anti-inflammatory effect of laser is blocked when corticosteroid receptors are downregulated (use of steroids)  
Lopes-Martins, Bjordal et al. 2006  
Photomed Laser Surg

## Laser in inflammation

### Animal studies

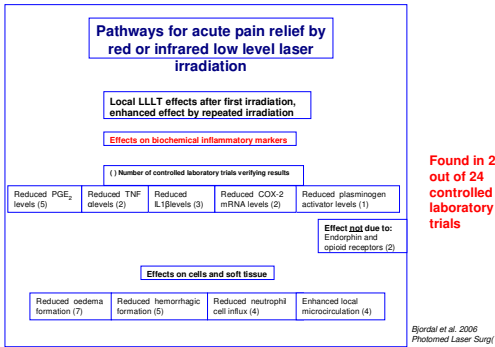


Anti-inflammatory effects similar to NSAID (celecoxib) in rat lung injury model  
Aimbre, Bjordal et al. 2007  
Photomed Laser Surg



Dose-dependent anti-inflammatory effect similar to NSAID (indomethacin) in rat knee OA model  
Lopes-Martins, Bjordal et al. (unpublished)

## Anti-inflammatory effects



## Laser therapy in Achille tendinitis

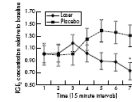
ORIGINAL ARTICLE

BJSM ONLINE

A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E<sub>2</sub> concentrations

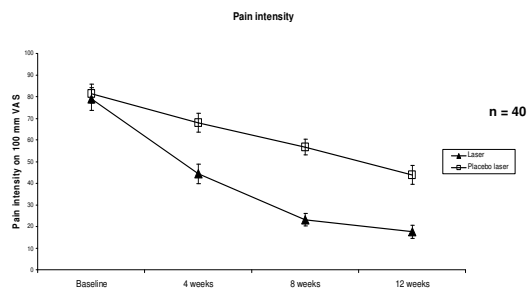
J M Bjordal, R A B Lopes-Martins, V V Iversen

Br J Sports Med 2006;40:76-80. doi: 10.1136/bjsm.2005.020842



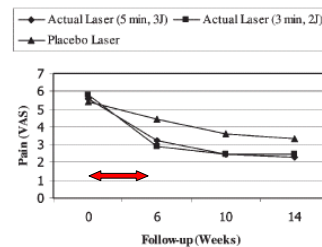
## Achillestendinopathy

### RCT with eccentric exercises and LLLT



## LLLT in knee osteoarthritis

LLLT and exercise therapy



# Health Technology Assessment in Norway

Nasjonalt kunnskapssenter for helsestjenesten

Report nr. 7/2004

## Effekt av fysioterapi ved kneleddsartrose, begrenset til elektroterapi og øvelsesbehandling

### 10.4 Results / Conclusions

Both knee land exercise and exercise led by a physical therapist improved pain, function and quality of life in patients with osteoarthritis of the knee. The exercise program must last for a minimum of eight weeks to give significant effects.

Most studies on exercise concentrate on strength training of the quadriceps and used 2-4 repetitions each week.

Both laser and TENS gave significant effects on pain relief at the end of treatment (2-4 weeks). However, the evidence for the effect by laser is weaker than for TENS.

Report 7/2004. Effect av fysioterapi ved artrosebehandling. Rapport til kunnskapssenteret for helsestjenesten

But how does physical interventions fare in comparison with recommended pharma interventions?

# Lack of updated evidence on drugs

Non-aspirin, non-steroidal anti-inflammatory drugs for treating osteoarthritis of the knee (Review)

Wenke M, Bouček ST, Fiebich A, Krivos J



THE COCHRANE COLLABORATION®

No comparisons of NSAIDs versus placebo

This version first published online 23 January 2006 in Issue 1, 2006.

Date of most recent submission assessment: 27 November 1996

The editorial group responsible for this previously published document have withdrawn it from publication.

REASON FOR WITHDRAWAL

Review has been withdrawn until an update can be undertaken to reflect the current evidence.

# A view from the outside in the cold northern loneliness



# Oral NSAIDs in knee OA

BMJ Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials

Jan Magnus Bjorndal, Anne Elisabeth Ljunggren, Atle Kløvning, Lars Skei

BMJ 2004;329:1317. originally published online 23 Nov 2004. doi:10.1136/bmj.32973.2004.055653



Withdrawal Symptoms

Patients, Doctors Explore Alternatives to Vioxx For Arthritis Relief -- Very Carefully

By January W. Payne  
Washington Post Staff Writer  
Tuesday, November 23, 2004; Page HE01

A new meta-analysis in the British Medical Journal (BMJ) recommends "only limited use" of NSAIDs for long-term treatment of knee osteoarthritis, citing questions about their effectiveness and safety. Of the 23 trials analyzed, all but one was short-term, evaluating the drugs' effects after two to 13 weeks. (The only longer-term study involved a drug not available in the United States.) A meeting of the Food and Drug Administration (FDA) drug safety advisory committee is planned for February to discuss the safety of the two other COX-2 drugs remaining on the U.S. market -- Bextra and Celebrex.

# Oral NSAIDs in knee OA

BMJ Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials

Jan Magnus Bjorndal, Anne Elisabeth Ljunggren, Atle Kløvning, Lars Skei

BMJ 2004;329:1317. originally published online 23 Nov 2004. doi:10.1136/bmj.32973.2004.055653

Table 2

Characteristics of trials of oral NSAIDs for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug (n = 994)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome time-points (in weeks; max. effect in bold)
Benson 99	Celecoxib-suppress	397	3	54.1	8.0 (2.5 to 13.7)	2, 6, 12
Cox 01	Ethorfenac	23	4	39.6	11.2 (6.2 to 17.2)	2, 12
Derrybell 05	Celecoxib	5	3	NA	11.2 (-12.7 to 31.7)	2
Drey 05	Naproxen-ethorfenac	168	3	NA	36.2 (4.8 to 27.7)	2, 4
Finckh 01	Robaximol	147	5	41.9	20.0 (15 to 25.5)	1, 2, 4, 6
Fischmann 07	Nabumetone-naproxen	182	3	39.9	9.2 (6.7 to 11.7)	2, 4
Gilchay 05	Celecoxib-robaximol	379	5	47.7	16.0 (14.4 to 19.0)	1, 6
Gonsky 02	Ethorfenac-diclofenac	236	3	46.4	18.0 (14.6 to 21.3)	1, 2, 4, 6
Leite 02	Celecoxib-suppress	40	5	71.9	3.2 (2.2 to 4.0)	2, 6, 12
Kristic 04	Robaximol-suppress	334	5	74.7	15.1 (4.9 to 25.3)	1, 6
Lar 03	Ethorfenac	27	3	37	2.5 (-2.9 to 7.8)	2, 6
Lehmann 05	Lumiracoxib	180	4	64.3	6.4 (4.2 to 8.6)	2, 4, 13
Lind 99	Meloxicam	134	3	46.2	6.6 (4.8 to 10.6)	1, 2, 3
McKinnon 01a	Celecoxib-diclofenac	400	3	49.1	8.9 (5.2 to 12.3)	2, 6
McKinnon 01b	Celecoxib-robaximol	122	3	72.0	14.5 (7.7 to 20.3)	2, 6
Schlienger 05	Nabumetone-ethorfenac	180	3	57.5	12.2 (5.4 to 21)	2, 4
Scott 06	Tamoxifen-acid	387	4	55.1	4.1 (4.0 to 4.2)	4
Shukla 05	Lumiracoxib-robaximol	1200	4	66.1	6.2 (3.9 to 9.7)	2, 4, 13
Steen 06	Celecoxib	222	4	67.6	6.0 (-1.5 to 12.1)	1, 2
Tammaraju 04	Ethorfenac-robaximol	1459	4	45.2	9.9 (8.6 to 11.2)	2, 4, 13
Tram 01	Ethorfenac-robaximol	226	3	41	17.0 (9.9 to 19.6)	4
Wasser 95	Nabumetone-naproxen	219	3	NA	12.5 (8.4 to 18.6)	1, 2, 4, 6
Williams 01	Celecoxib	472	4	66.4	7.2 (2.9 to 12.1)	2, 6
Williams 09	Ethorfenac	30	3	76	7.5 (0.8 to 14.6)	2, 4
Zhao 09	Celecoxib	397	5	13.9	7.2 (4.8 to 9.2)	2, 12
Overall		994	3.8*	64.3*	8.2 (8.8 to 11.6)	2.8*

NA, not available.

\* Mean.

† Weighted mean.

# Patient selection criteria inflates effect estimate in oral NSAID trials

Patients recruited from ongoing phase IV NSAID trial

Patients not tolerating NSAIDs are already excluded

Patients required to stop taking NSAID for 3-7 days

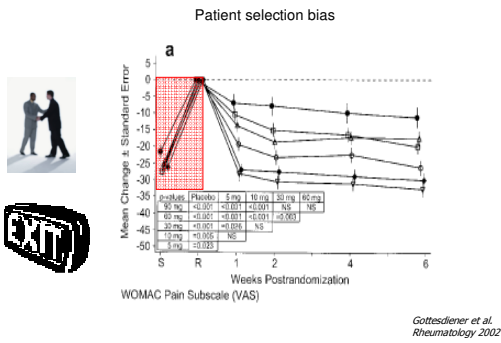


Patients required to have at least 40 mm pain on VAS

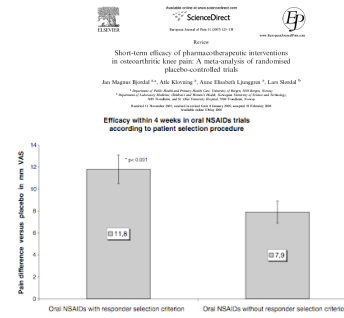
Patients required to have at least 15 mm pain increase on VAS after stopping with NSAID

Patients not responding to NSAIDs are already excluded

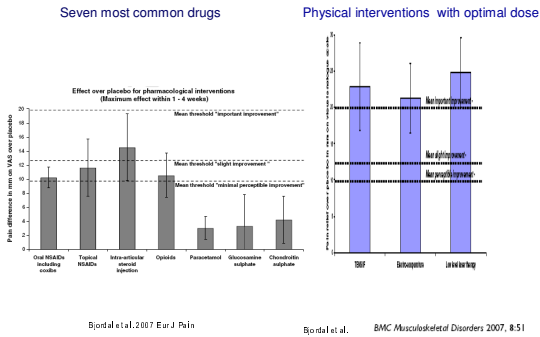
## Recruitment of patients to NSAID-trials



## Selection bias in knee osteoarthritis NSAID trials



## Comparison between drugs and LLLT in KOA

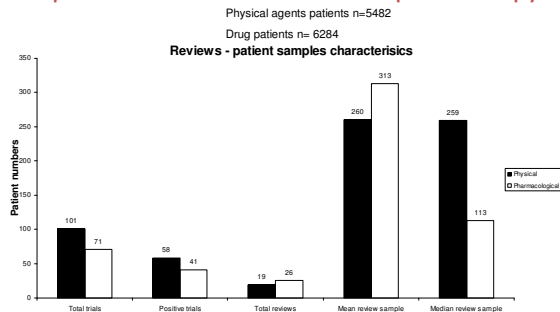


## Is LLLT and physical agents evaluated differently from drugs in the Cochrane Library?

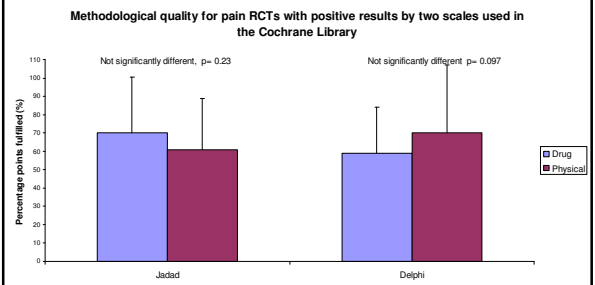
Analysis of Cochrane reviews of randomized placebo-controlled trials with pain therapy



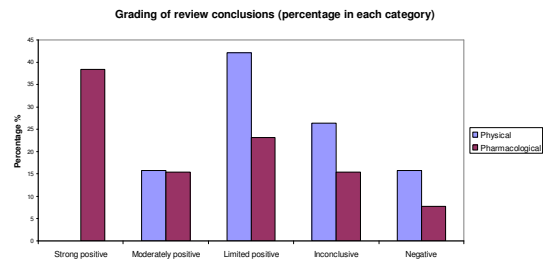
## Analysis of Cochrane reviews of randomized placebo-controlled trials with pain therapy



## Analysis of Cochrane reviews of randomized placebo-controlled trials with pain therapy



## Analysis of Cochrane reviews of randomized placebo-controlled trials with pain therapy



# Thank You!



Bergen - Norway