•From Evidence based medicine to evidence based practice: Is there a paradox in the international recommendations in osteoarthritis?

Pr Xavier Chevalier
CHU Henri Mondor
Créteil

« Without the freedom of criticism, there is no eloge flaterring »Voltaire

Consensus

- Non pharmalogical issue as the first step of the treatment

- Association of non pharmacological + pharmacological therapies

Chevalier X et al. Ann Rheum Dis 2011
Chevalier X , Migliore Eur J Inflammation ; 2013; 11

Divergences in recommandations

	ACR	EULAR	OARSI	NICE	AAOS
Acetaminophen	+	+	+	-	+
NSAIDs	+	+	+	+	+
SySADOA	-	+	?	-	+
Opioids	±	±	?	±	NA
CS i.a	+	+	+	+	+
HA i.a	-	+	?	-	-
Acupuncture	+	+	?	-	-
Lavage	-	-	-	-	+

?= incertain

Nice 2013

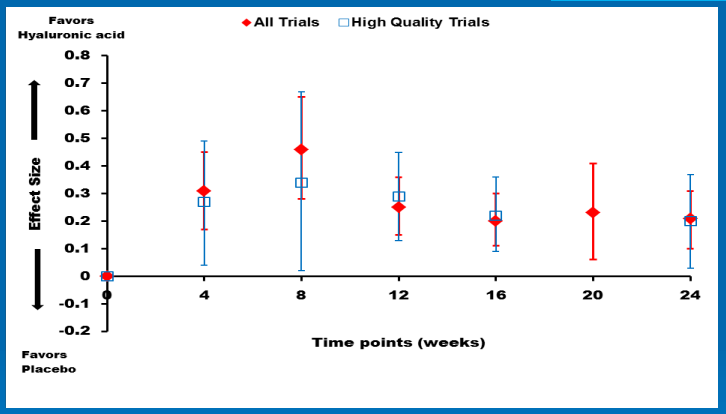
CS=Corticosteroids
HA=Hyaluronic Acid

How to interpret all those puzzling recommendations: The HA example?

Effect size of HA: Missing and/or mixing data

HA: Puzzling results of 12 meta-analysis

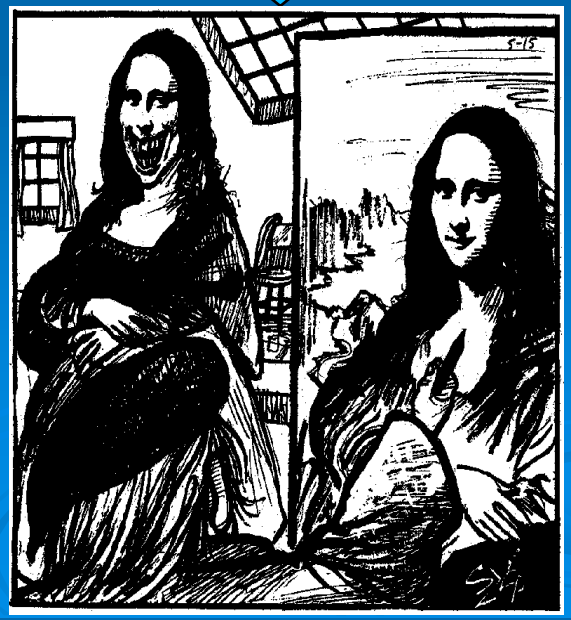
71 trials (9617 patients):
weak effect on pain
ES: -0.37 (95% CI, -0.46 to -0.28), month 3
18 large RC trials
(5094 patients) effect non significant
ES: -0.11 (CI, -0.18 to -0.04), month 3
Rutjes AW et al. Ann Intern med 2012 june



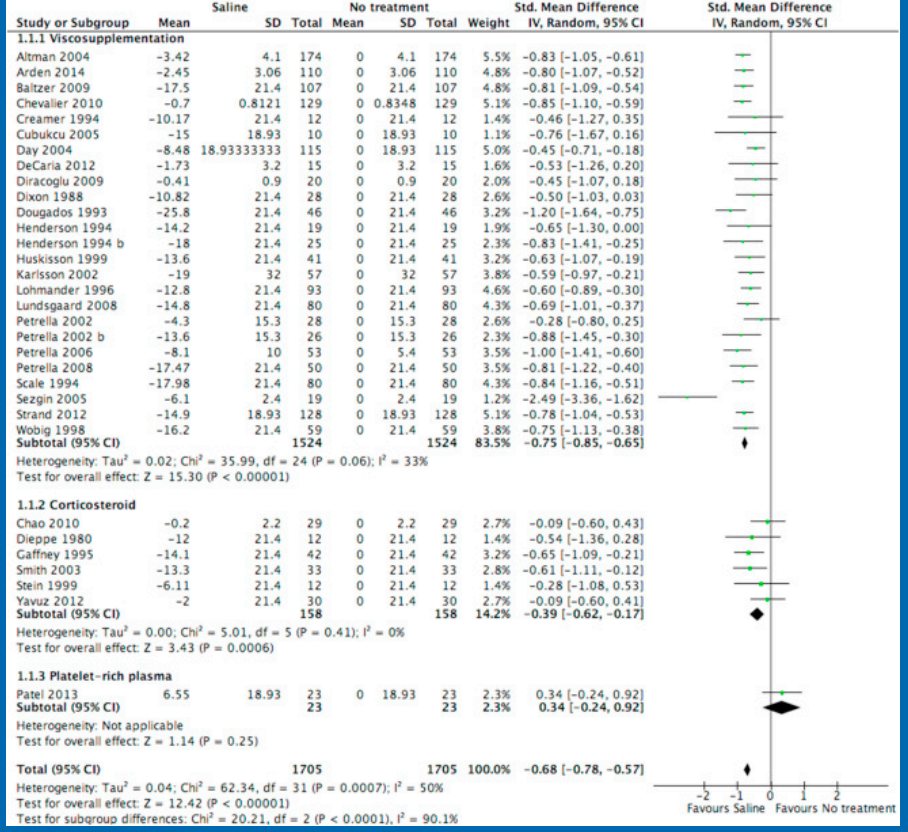
Selection of high quality trials
ET: 0.20
RMD open Richette P et al

ES: 0,46,month 2
ES: 0.29 month 3

Banurru . Osteoarthritis Cartilage 2011;19 :611-9.



Comparison AH, CS, PRP vs placebo



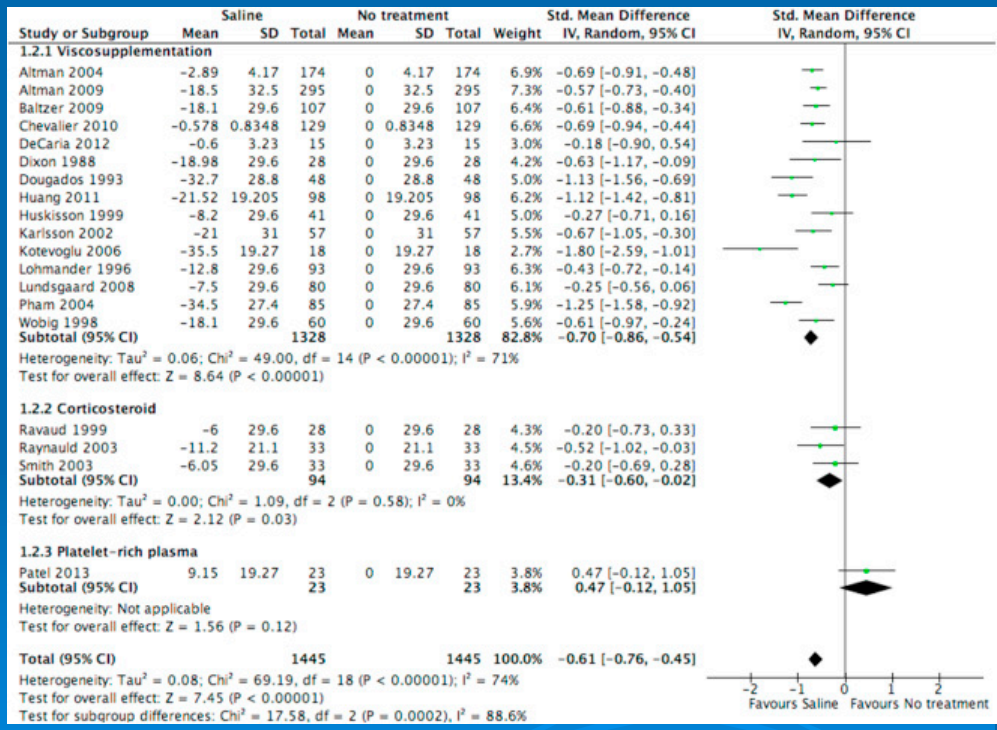
Study or Subgroup	Saline Mean	SD	Total	No treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Viscosupplementation								
Altman 2004	-3.42	4.1	174	0	4.1	174	5.5%	-0.83 [-1.05, -0.61]
Arden 2014	-2.45	3.06	110	0	3.06	110	4.8%	-0.80 [-1.07, -0.52]
Baltzer 2009	-17.5	21.4	107	0	21.4	107	4.8%	-0.81 [-1.09, -0.54]
Chevalier 2010	-0.7	0.8121	129	0	0.8348	129	5.1%	-0.85 [-1.10, -0.59]
Creamer 1994	-10.17	21.4	12	0	21.4	12	1.4%	-0.46 [-1.27, 0.35]
Cubukcu 2005	-15	18.93	10	0	18.93	10	1.1%	-0.76 [-1.67, 0.16]
Day 2004	-8.48	18.93333333	115	0	18.93	115	5.0%	-0.45 [-0.71, -0.18]
DeCaria 2012	-1.73	3.2	15	0	3.2	15	1.6%	-0.53 [-1.26, 0.20]
Diracoglu 2009	-0.41	0.9	20	0	0.9	20	2.0%	-0.45 [-1.07, 0.18]
Dixon 1988	-10.82	21.4	28	0	21.4	28	2.6%	-0.50 [-1.03, 0.03]
Dougados 1993	-25.8	21.4	46	0	21.4	46	3.2%	-1.20 [-1.64, -0.75]
Henderson 1994	-14.2	21.4	19	0	21.4	19	1.9%	-0.65 [-1.30, 0.00]
Henderson 1994 b	-18	21.4	25	0	21.4	25	2.3%	-0.83 [-1.41, -0.25]
Huskisson 1999	-13.6	21.4	41	0	21.4	41	3.2%	-0.63 [-1.07, -0.19]
Karlsson 2002	-19	32	57	0	32	57	3.8%	-0.59 [-0.97, -0.21]
Lohmander 1996	-12.8	21.4	93	0	21.4	93	4.6%	-0.60 [-0.89, -0.30]
Lundsgaard 2008	-14.8	21.4	80	0	21.4	80	4.3%	-0.69 [-1.01, -0.37]
Petrella 2002	-4.3	15.3	28	0	15.3	28	2.6%	-0.28 [-0.80, 0.25]
Petrella 2002 b	-13.6	15.3	26	0	15.3	26	2.3%	-0.88 [-1.45, -0.30]
Petrella 2006	-8.1	10	53	0	5.4	53	3.5%	-1.00 [-1.41, -0.60]
Petrella 2008	-17.47	21.4	50	0	21.4	50	3.5%	-0.81 [-1.22, -0.40]
Scale 1994	-17.98	21.4	80	0	21.4	80	4.3%	-0.84 [-1.16, -0.51]
Sezgin 2005	-6.1	2.4	19	0	2.4	19	1.2%	-2.49 [-3.36, -1.62]
Strand 2012	-14.9	18.93	128	0	18.93	128	5.1%	-0.78 [-1.04, -0.53]
Wobig 1998	-16.2	21.4	59	0	21.4	59	3.8%	-0.75 [-1.13, -0.38]
Subtotal (95% CI)			**1524**			**1524**	**83.5%**	**-0.75 [-0.85, -0.65]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 35.99$, df = 24 (P = 0.06); $I^2 = 33\%$								
Test for overall effect: Z = 15.30 (P < 0.00001)								
1.1.2 Corticosteroid								
Chao 2010	-0.2	2.2	29	0	2.2	29	2.7%	-0.09 [-0.60, 0.43]
Dieppe 1980	-12	21.4	12	0	21.4	12	1.4%	-0.54 [-1.36, 0.28]
Gaffney 1995	-14.1	21.4	42	0	21.4	42	3.2%	-0.65 [-1.09, -0.21]
Smith 2003	-13.3	21.4	33	0	21.4	33	2.8%	-0.61 [-1.11, -0.12]
Stein 1999	-6.11	21.4	12	0	21.4	12	1.4%	-0.28 [-1.08, 0.53]
Yavuz 2012	-2	21.4	30	0	21.4	30	2.7%	-0.09 [-0.60, 0.41]
Subtotal (95% CI)			**158**			**158**	**14.2%**	**-0.39 [-0.62, -0.17]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.01$, df = 5 (P = 0.41); $I^2 = 0\%$								
Test for overall effect: Z = 3.43 (P = 0.0006)								
1.1.3 Platelet-rich plasma								
Patel 2013	6.55	18.93	23	0	18.93	23	2.3%	0.34 [-0.24, 0.92]
Subtotal (95% CI)			**23**			**23**	**2.3%**	**0.34 [-0.24, 0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.25)								
Total (95% CI)			**1705**			**1705**	**100.0%**	**-0.68 [-0.78, -0.57]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 62.34$, df = 31 (P = 0.0007); $I^2 = 50\%$								
Test for overall effect: Z = 12.42 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 20.21$, df = 2 (P < 0.0001), $I^2 = 90.1\%$								

Std. Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Favours Saline Favours No treatment

Standardized mean differences, short-term pain (≤3 months) from baseline



Study or Subgroup	Saline Mean	SD	Total	No treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Viscosupplementation								
Altman 2004	-2.89	4.17	174	0	4.17	174	6.9%	-0.69 [-0.91, -0.48]
Altman 2009	-18.5	32.5	295	0	32.5	295	7.3%	-0.57 [-0.73, -0.40]
Baltzer 2009	-18.1	29.6	107	0	29.6	107	6.4%	-0.61 [-0.88, -0.34]
Chevalier 2010	-0.578	0.8348	129	0	0.8348	129	6.6%	-0.69 [-0.94, -0.44]
DeCaria 2012	-0.6	3.23	15	0	3.23	15	3.0%	-0.18 [-0.90, 0.54]
Dixon 1988	-18.98	29.6	28	0	29.6	28	4.2%	-0.63 [-1.17, -0.09]
Dougados 1993	-32.7	28.8	48	0	28.8	48	5.0%	-1.13 [-1.56, -0.69]
Huang 2011	-21.52	19.205	98	0	19.205	98	6.2%	-1.12 [-1.42, -0.81]
Huskisson 1999	-8.2	29.6	41	0	29.6	41	5.0%	-0.27 [-0.71, 0.16]
Karlsson 2002	-21	31	57	0	31	57	5.5%	-0.67 [-1.05, -0.30]
Kotevoglu 2006	-35.5	19.27	18	0	19.27	18	2.7%	-1.80 [-2.59, -1.01]
Lohmander 1996	-12.8	29.6	93	0	29.6	93	6.3%	-0.43 [-0.72, -0.14]
Lundsgaard 2008	-7.5	29.6	80	0	29.6	80	6.1%	-0.25 [-0.56, 0.06]
Pham 2004	-34.5	27.4	85	0	27.4	85	5.9%	-1.25 [-1.58, -0.92]
Wobig 1998	-18.1	29.6	60	0	29.6	60	5.6%	-0.61 [-0.97, -0.24]
Subtotal (95% CI)			**1328**			**1328**	**82.8%**	**-0.70 [-0.86, -0.54]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 49.00$, df = 14 (P < 0.00001); $I^2 = 71\%$								
Test for overall effect: Z = 8.64 (P < 0.00001)								
1.2.2 Corticosteroid								
Ravaud 1999	-6	29.6	28	0	29.6	28	4.3%	-0.20 [-0.73, 0.33]
Raynauld 2003	-11.2	21.1	33	0	21.1	33	4.5%	-0.52 [-1.02, -0.03]
Smith 2003	-6.05	29.6	33	0	29.6	33	4.6%	-0.20 [-0.69, 0.28]
Subtotal (95% CI)			**94**			**94**	**13.4%**	**-0.31 [-0.60, -0.02]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 2 (P = 0.58); $I^2 = 0\%$								
Test for overall effect: Z = 2.12 (P = 0.03)								
1.2.3 Platelet-rich plasma								
Patel 2013	9.15	19.27	23	0	19.27	23	3.8%	0.47 [-0.12, 1.05]
Subtotal (95% CI)			**23**			**23**	**3.8%**	**0.47 [-0.12, 1.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.56 (P = 0.12)								
Total (95% CI)			**1445**			**1445**	**100.0%**	**-0.61 [-0.76, -0.45]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 69.19$, df = 18 (P < 0.00001); $I^2 = 74\%$								
Test for overall effect: Z = 7.45 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 17.58$, df = 2 (P = 0.0002), $I^2 = 88.6\%$								

Std. Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Favours Saline Favours No treatment

Standardized mean differences, long-term pain (6–12 months) from baseline

Altman Rd et al. Seminars in Arthritis and Rheumatism, 2016, Available online 27 April 2016

Meta analysis of meta analysis

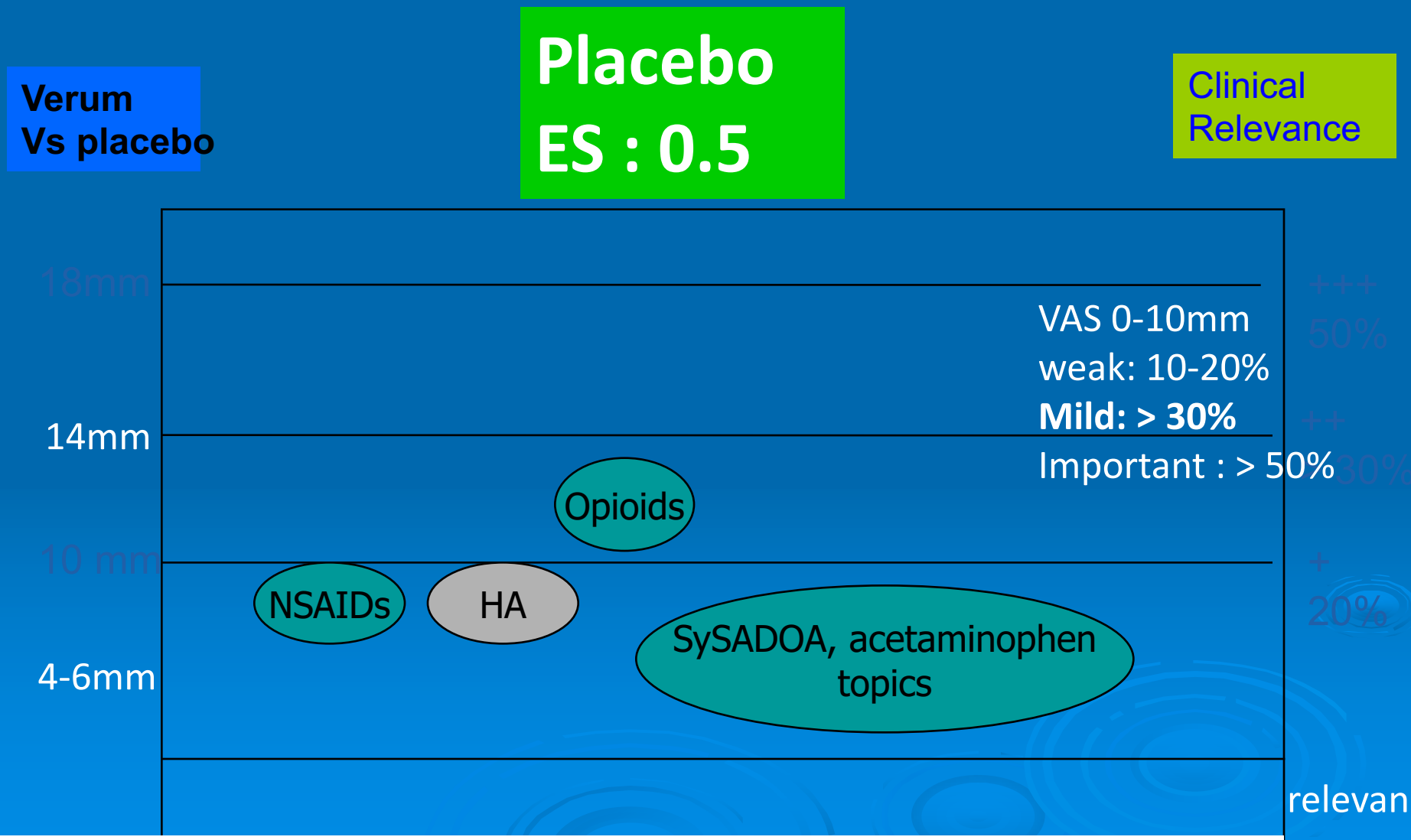
- **Currently, the best evidence suggested that HA is an effective intervention in treating knee**

Xing, D. *et al*. Intra-articular Hyaluronic Acid in Treating Knee Osteoarthritis: a PRISMA-Compliant Systematic Review of Overlapping Meta-analysis. *Sci. Rep.* 6, 32790; doi: 10.1038/srep32790 (2016).

How to interpret all those puzzling recommendations

Effect size: should take into account the placebo effect in OA

Comparison of treatments vs placebo in OA



Recommandations IMMPACT: Bjordal JM et al. Eur J Pain 2007; Dworkin RH, Arthritis Rheum 2014, Gewandter JS; Pain 2014; O Connor AB .Pain 2013

Chronic pain in OA: moving from the joint to the head !

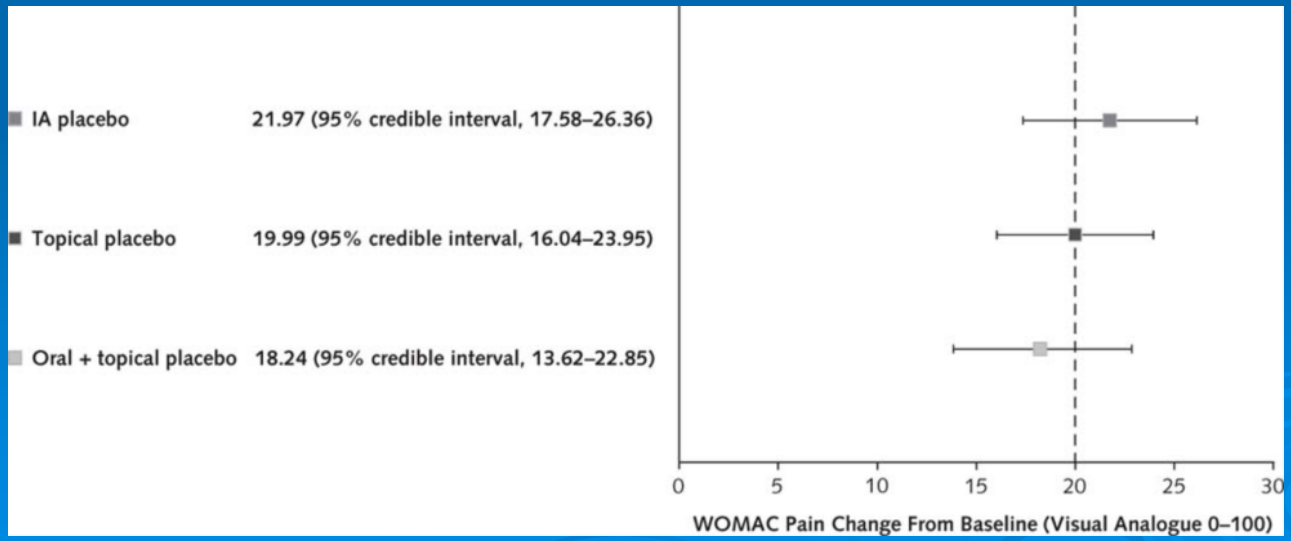
Munch, Oslo Museum

Articular puncture and saline injection: A placebo or not a placebo ?

Table. Standardized Mean Differences (Adjusted for Small Samples) for Pain at 3 Mo*

Comparators	Placebos		
	Oral Plus Topical Placebo	Topical Placebo	Intra-articular Placebo
Oral placebo	0.12 (−0.09 to 0.33)	0.20† (0.02 to 0.38)	0.29† (0.09 to 0.49)
Oral plus topical placebo	-	0.08 (−0.16 to 0.31)	0.17 (−0.11 to 0.44)
Topical placebo	-	-	0.09 (−0.17 to 0.35)

* Values are standardized mean differences (95% credible intervals). Effect sizes favor the above (column heading) intervention in each comparison vs. the left-hand intervention (row label).
† Statistically significant effect sizes.



Bannuru R et al. Ann Intern Med. 2015;163(5):365-372. doi:10.7326/M15-0623

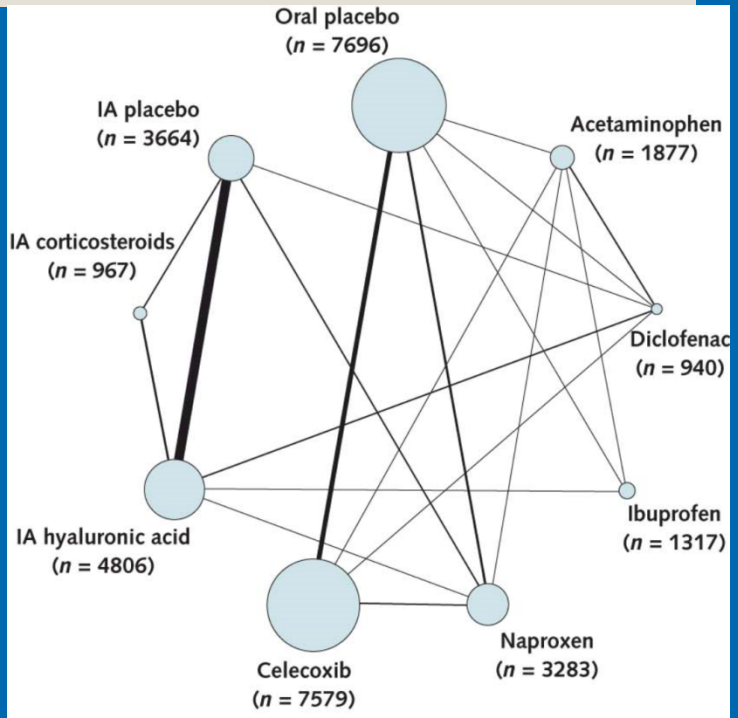
A small effect over placebo is still better than placebo

How to interpret all those puzzling recommendations

Alternate pharmacological options: the efficacy issue

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Ann Intern Med. 2015;162(1):46-54. doi:10.7326/M14-1231



Comparisons	Trials, *n*
Oral placebo vs. acetaminophen	6
Oral placebo vs. diclofenac	6
Oral placebo vs. ibuprofen	5
Oral placebo vs. naproxen	14
Oral placebo vs. celecoxib	28
Acetaminophen vs. diclofenac	2
Acetaminophen vs. ibuprofen	2
Acetaminophen vs. naproxen	1
Acetaminophen vs. celecoxib	4
Diclofenac vs. celecoxib	1
Diclofenac vs. IA hyaluronic acid	2
Diclofenac vs. IA placebo	2
Ibuprofen vs. IA hyaluronic acid	1
Naproxen vs. celecoxib	7
Naproxen vs. IA haluronic acid	1
Naproxen vs. IA placebo	2
IA Hyaluronic acid vs. IA corticosteroids	12
IA Hyaluronic acid vs. IA placebo	52
IA Corticosteroids vs. IA placebo	7

Figure Legend:

Network of treatment comparisons for pain.
Circle size reflects number of participants,
and the line width reflects the number of direct comparisons.
No connecting line between 2 treatments indicates that there was no direct comparison. IA = intra-articular.

Network Meta-analysis (ES at 3 months)

	COMPARATOR	
TREATMENT	ES / Placebo oral	ES / Placebo IA
Paracetamol	0,18 (0,04 à 0,33)	-0,11 (-0,38 à 0,17)
Placebo IA	0,29 (0,04 à 0, 54)	-
Celecoxib	0,33 (0,25 à 0,42)	0,04 (0,21 à 0,30)
Naproxene	0,38 (0,27 à 0,49)	0,09 (-0,15 à 0,34)
Diclofenac	0,52 (0,34 à 0,69)	0,23 (-0,03 à 0,49)
Corticosteroids IA	0,61 (0,32 à 0,89)	0,32 (0,16 à 0,47)
HA IA	**0,63 (0,39 à 0,88)**	**0,34 (0,26 à 0, 42)**

- **Intra articular therapies > NSAIDs**
- **The most efficient Treatment is HA**

Bannuru et al. Ann Inter Med 2015

How to interpret all those puzzling recommendations

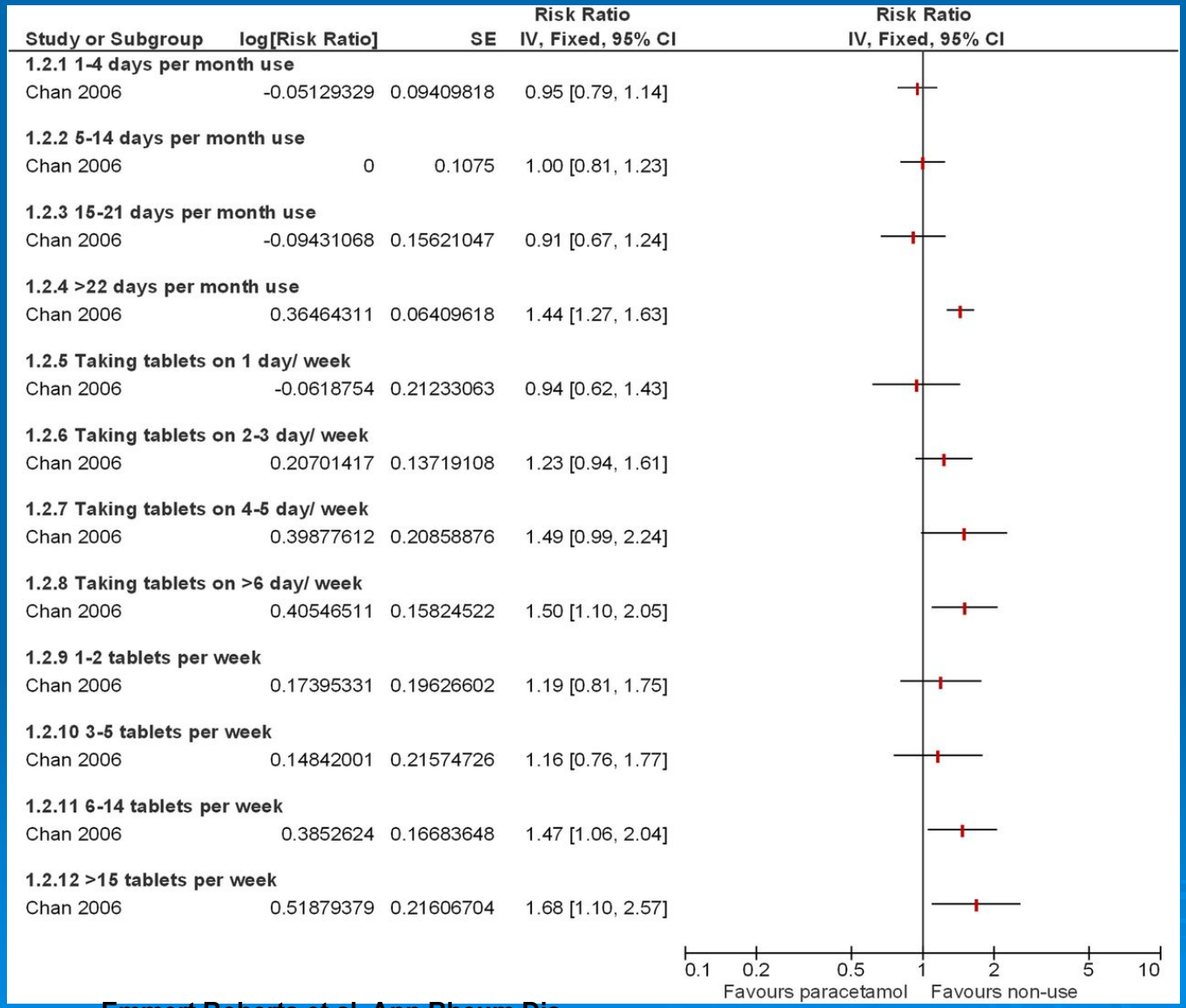
Alternate pharmacological options: the safety issue

Acetaminophen: A Good boy….

- First cause of hepatic failure [1]
- Cardiovascular toxicity[2]
- Digestive toxicity[2]
- Renal disease[3]

1. Craig DG et al Br J Clin Pharmacol. 2012 Feb;73(2):285-94
2. Hinz B et al. Ann Rheum Dis 2012 Jan 71:20-25
3. Kelkar et al. J Manag Care Pharm 2012 ;18:234-46

Cardiovascular adverse events (AEs)



Emmert Roberts et al. Ann Rheum Dis
doi:10.1136/annrheumdis-2014-206914

ARD

How to interpret all those puzzling recommendations: The HA example?

Is there any risk in excluding HA ?

What is the risk in excluding therapeutical options such HA?

- **Increase the risk of intake of other drugs with a worse safety profile**
- **Increase intake of the rescue alternates non validated medicines and diets**
- **Increase the risk of total joint replacement**
- **Increase the feeling of patients of a neglected disease**
- **Increase the cost of others therapies and the risk of hospitalizations**

- Opioid abuse has reached epidemic proportions in the United States and accounted for 28 000 deaths in 2014

- Ray WA et al. JAMA. 2016;315(22):2415-2423

From: **Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain**

Ray WA et al. JAMA. 2016;315(22):2415-2423. doi:10.1001/jama.2016.7789

Table 3. Mortality According to Underlying Cause of Death

	Anticonvulsant or Cyclic Antidepressant (Person-Years of Follow-up = 8066)		Long-Acting Opioid (Person-Years of Follow-up = 11 070)				
Deaths	Deaths	Incidence per 10 000 Person-Years	Deaths	Incidence per 10 000 Person-Years	Adjusted Hazard Ratio (95% CI)[a]	Adjusted Risk Difference (95% CI)[a,b]	*P* Value
All	87	107.9	185	167.1	1.64 (1.26 to 2.12)	68.5 (28.2 to 120.7)	<.001
Out-of-hospital	60	74.4	154	139.1	1.90 (1.40 to 2.58)	67.1 (30.1 to 117.3)	<.001
Unintentional overdose[c]	7	8.7	34	30.7	3.37 (1.47 to 7.70)	20.6 (4.1 to 58.1)	.004
Other causes	53	65.7	120	108.4	1.72 (1.24 to 2.39)	47.4 (15.7 to 91.4)	.001
Cardiovascular	36	44.6	79	71.4	1.65 (1.10 to 2.46)	28.9 (4.6 to 65.3)	.02
Respiratory	3	3.7	10	9.0	3.00 (0.81 to 11.09)	7.4 (−0.7 to 37.5)	.10
Other injury	11	13.6	19	17.2	1.15 (0.54 to 2.47)	2.1 (−6.3 to 20.0)	.72
Other	3	3.7	12	10.8	3.72 (1.04 to 13.30)	10.1 (0.2 to 45.7)	.04
Hospital	27	33.5	31	28.0	1.00 (0.59 to 1.69)	0 (−13.6 to 23.1)	>.99

[a] Adjusted for baseline propensity score decile, age, and calendar year during follow-up.

[b] Risk differences for the specific causes of death do not sum because the regression model parameters are estimated separately for each cause.

[c] The cohort excluded patients with a diagnosis of or procedure for treatment of substance abuse other than nicotine or alcohol as well as those prescribed buprenorphine. Because such patients would plausibly have increased risk of overdose, overdose mortality in the study cohort is likely to be lower than that in a more general patient population.

Mortality According to Underlying Cause of Death

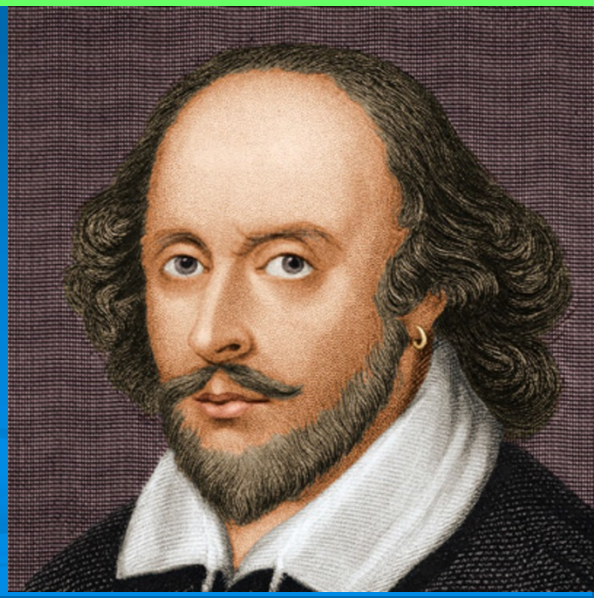
Retrospective cohort study included Tennessee Medicaid,1999-2012

How to interpret all those puzzling recommendations

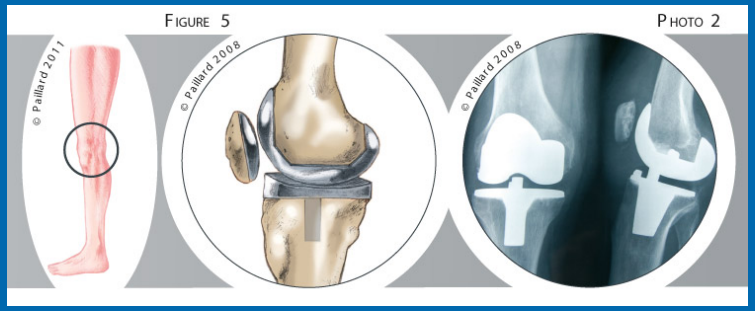
« A lot of noise for nothing »

W. Shakespeare

The Final issue is the TKR: No joint=No pain



- Total Knee Replacement
- NO JOINT = NO PAIN ?



THE JOURNAL OF BONE & JOINT SURGERY (BR)

Predicting dissatisfaction following total knee replacement

A PROSPECTIVE STUDY OF 1217 PATIENTS

C. E. H. Scott,
C. R. Howie,
D. MacDonald,
L. C. Biant

From Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Up to 20% of patients are not satisfied with the outcome following total knee replacement (TKR). This study investigated the pre- and post-operative predictors of dissatisfaction in a large cohort of patients undergoing TKR. We assessed 1217 consecutive patients between 2006 and 2008 both before operation and six months after, using the Short-form (SF)-12 health questionnaire and the Oxford Knee Score. Detailed information concerning comorbidity was also gathered. Satisfaction was measured at one year when 18.6% (226 of 1217) of patients were unsure or dissatisfied with their replacement and 81.4% (911 of 1217) were satisfied or very satisfied. Multivariate regression analysis was performed to identify independent predictors of dissatisfaction. Significant ($p < 0.001$) predictors at one year included the pre-operative SF-12 mental component score, depression and pain in other joints, the six-month SF-12 score and poorer improvement in the pain element of the Oxford Knee Score.

Patient expectations were highly correlated with satisfaction. Satisfaction following TKR is multifactorial. Managing the expectations and mental health of the patients may reduce dissatisfaction. However, the most significant predictor of dissatisfaction is a painful total knee replacement.

Scott CEH . JBJS. & Nilsdotter A-K, Toksvig-Larsen S, Roos EM. A 5 year prospective study of patient-relevant outcomes after total knee replacement. Osteoarthr Cartil. 2009;17:601–6

Whats is the risk in excluding several therapeutical options ?

To increase the feeling of patients of a neglected disease ?

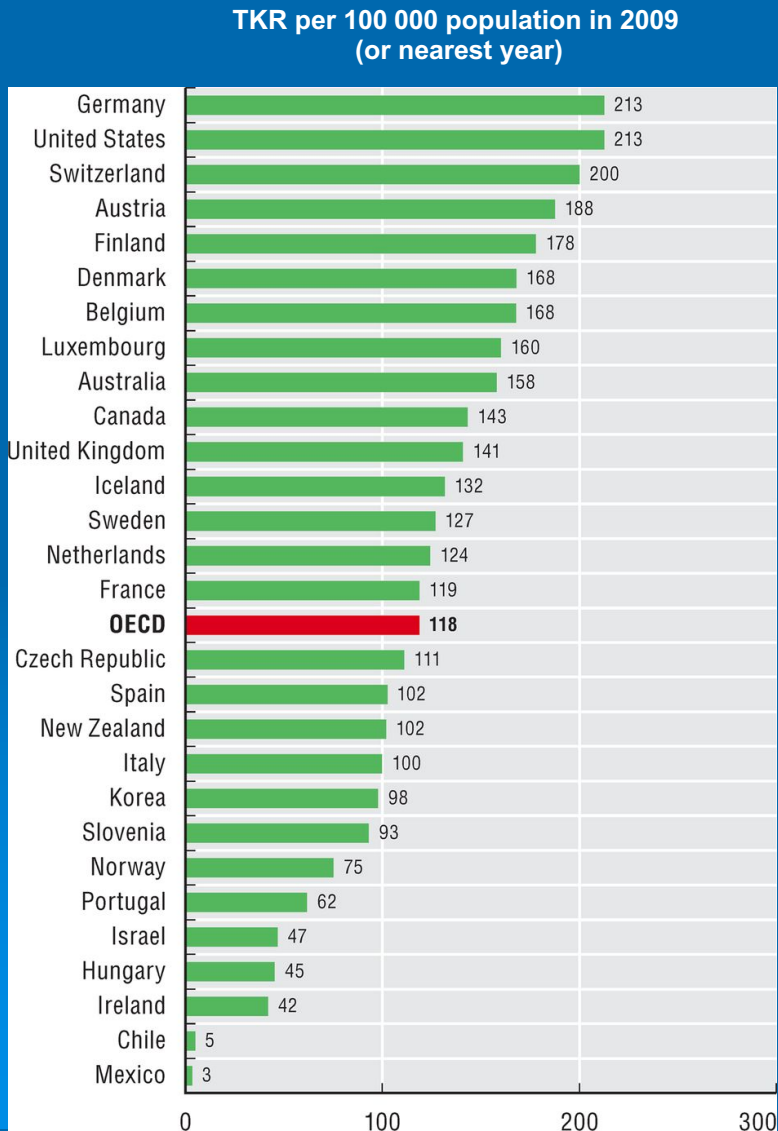
Physicians
4- Physicians underestimate pain in knee osteoarthritis

Benhamou M, et al .PLoS One. 2013;8(1):e53886

Whats is the risk in excluding several therapeutical options : The cost

- **Costs related to NSAIDs side effects are considerable, as well as costs related to joint replacement**
- **Both direct costs related to intervention and costs related to adverse events**

USA: the number of TKR is projected to increase to 3 000 000 per year by 2030, estimated cost of US$45 billion



Pelletier J et al. Ann Rheum Dis 2013;72:1594-1604

Gap between daily practice (EBP) and conference consensus (EBM):

why ?

The gap: The 5 commandments

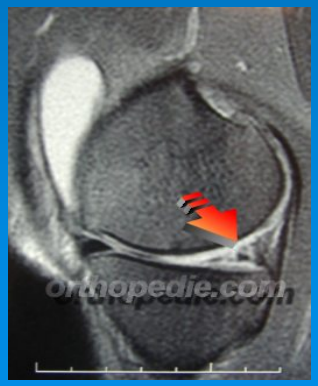
- **The « ideal patient » in clinical trials differs from the one seen in real life**
- **The phenotype of pain may differ from one individual to other**
- **The phenotype of pain may differ in the same individual**
- **The level of response for one drug may differ overtime**
- **The recommendations consider one therapy at a given time as opposed to the sum of different therapies used in daily pratice +++**

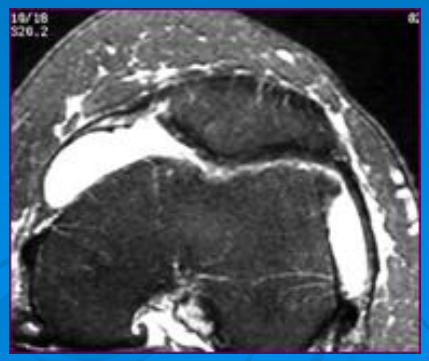
Castaneda S et al. Rheumatology 2014

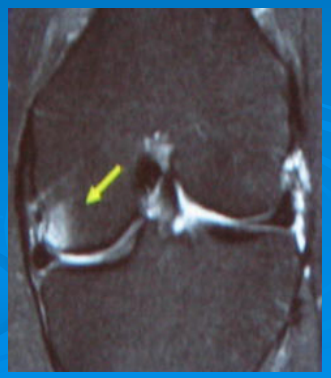
Pain fluctuates over time

Pain in OA: not a unique cause

. Synovial Inflammatory flare
. Bone pain (BML)
. Meniscal pain
. Ligament pain
. Muscle pain and pain related to instability
. Neuropathic component







Mentalities are changing

Commentary on recent therapeutic guidelines for osteoarthritis.

- **«Discrepancies between guidelines are few and mostly reflect heterogeneity of expert panels involved, geographical differences in the availability of pharmacotherapies, and heterogeneity of the studies included. Panels chosen for guideline development should include experts with real clinical experience in drug use and patient management»**

- **«Harmonization of the recommendations for knee OA treatment is challenging but feasible, as shown by the step-by-step therapeutic algorithm developed by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)»**

Cutolo M. Berenbaum F, Hochberg M, Punzi L, Reginster JY. Sem Arthritis Rheum Dec 2014

Migliore A, Bizzi E, Herrero-Beaumont J, Petrella RJ, Raman R, Chevalier X. Eur Rev Med Pharmacol Sci. 2015;19(7):1124-9

CONCLUSIONS

- International recommendations are useful

But

- International recommendations are not sufficient …
- It is not a Bible nor a cooking book
- They should be adapted at an individual level