One-fits-all war Gestern!

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Disclosures

Bart Morlion, MD, PhD

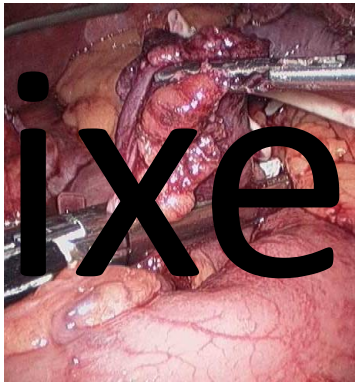
- I'm registered with the Belgian transparency register(Sunshine Act; beTransparent)
- I have interactions with the pharmaceutical industry related to the development and clinical evaluation of analgesics, but receive no royalty (cash or otherwise) from sales
- I do not own shares from these companies
- Over the past 5 years, I received grants and/or honoraria for:
  - Clinical research: Novartis, Pfizer, Janssen, Shionogi
  - Speaker's activities: Grünenthal, Kyowa-Kirin, Lilly, Mundipharma, Pfizer, P&G
  - Consultancy activities: Astellas, Boehringer Ingelheim, Grünenthal, Janssen, Mundipharma, TEVA, GSK, Kyowa-Kirin, Pfizer, Lilly, Boston Scientific

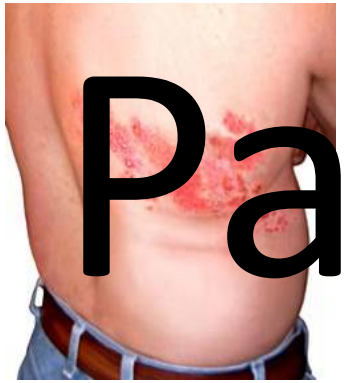
https://www.betransparent.be/en/ [accessed 17th July 2019]

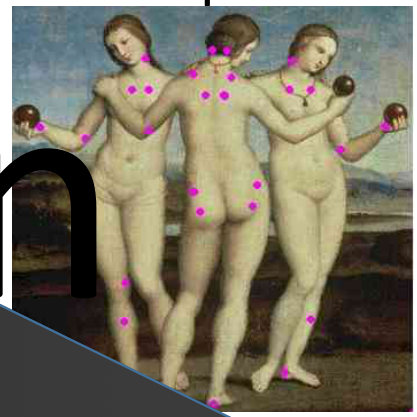
Mixed ?
Going nuts ?

Clinical Pain Syndromes

Nociceptive | Inflammatory | Neuropathic | Nociplastic







Mixed Pain

Noxious stimuli | Inflammation | timuli

High Threshold | **Low Threshold**

ms | s to h

Adapted from Woolf C. Ann Intern Med. 2004;140:441-451; Kose et al. PAIN 157 (2016) 1382–1386

No Mixed Pain !

https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698 Assessed 24 August 2019

ICD-11 for Mortality and Morbidity Statistics

World Health Organization

ICD-11 Update

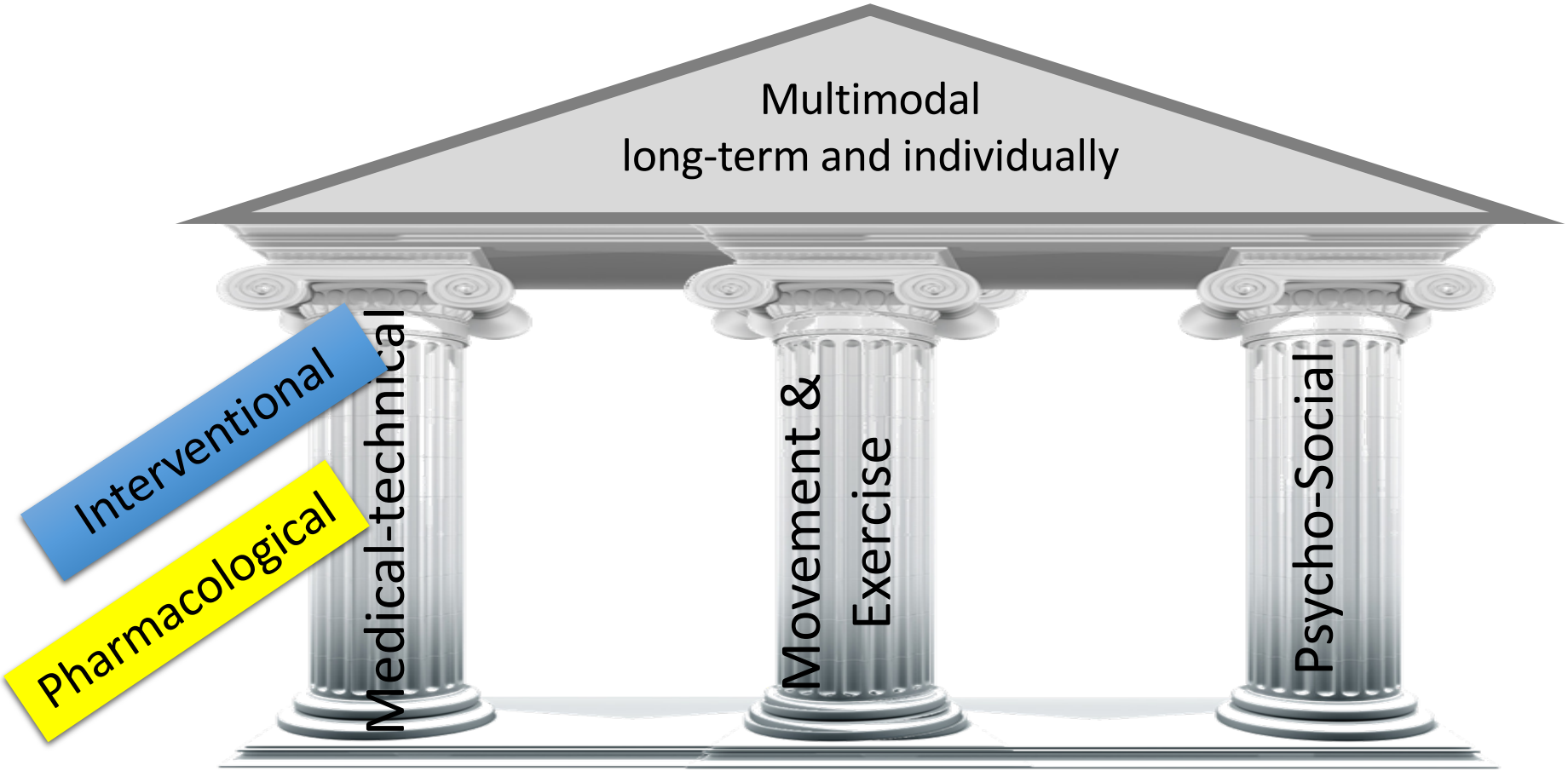
No Mixed Pain !

MG30 Chronic pain

MG30.0	Chronic primary pain
MG30.1	Chronic cancer related pain
MG30.2.	Chronic postsurgical or posttraumatic pain
MG30.3	Chronic secondary musculoskeletal pain
MG30.4	Chronic secondary visceral pain
MG30.5	Chronic neuropathic pain
MG30.6	Chronic secondary headache or orofacial pain
MG30.Y	Other specified chronic pain
MG30.Z	Chronic pain, unspecified

https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1581976053 Assessed 24 August 2019

Management of Pain

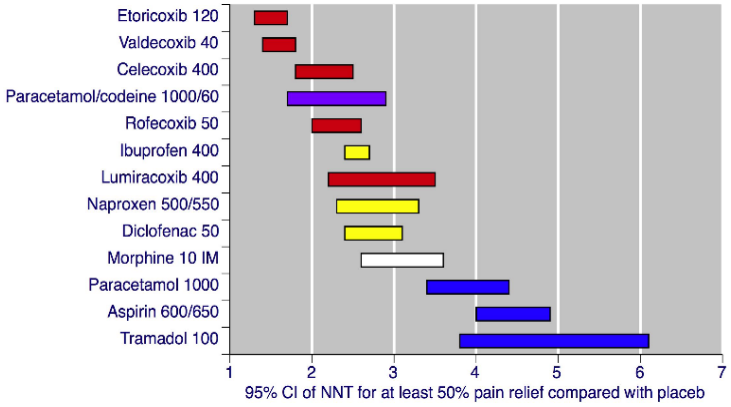


Adapted from Morlion B. . Nat. Rev. Neurol. 462-473 (2013)

Pharmacotherapy of pain

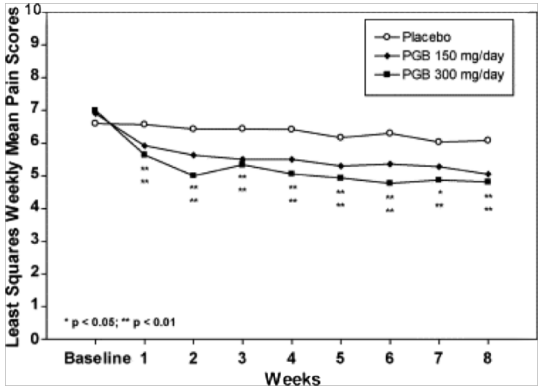
Acute pain

- Mostly inflammatory and nociceptive mechanisms[1]
- Paracetamol/NSAIDs/COXIBs/opioids[1]
- **NNT: 1.5-2.5**



Chronic pain

- More neuropathic and nociplastic mechanisms (mixed ?)
- Only 40–60% of patients reach 30% pain relief[2]
- Average improvements ranging from <10 to 20 mm VAS versus placebo[3]
- More atypical analgesics[2,4]
  - Antidepressants, anticonvulsants, NMDA antagonists, opioids, alpha 2 agonists, capsaicin etc
- **NNT: 4->10**



1. Moore et al. Cochrane Database Syst Rev. 2015;4:CD010794; 2. Dworkin et al. Pain. 2007;132:237; 3. Dworkin et al. Pain. 2011;152:S107; 4. Attal and Bouhassira. Pain. 2015;156(Suppl 1):S104; 5. Oxford League Table of analgesics in acute pain - http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/Leagtab.html [accessed 17th July 2019]Figure on the right: Sabatowski R. et al. Pain 109 (2004) 26-35

Pharmacotherapy of Neuropathic Pain
NNTs and quality of evidence

Treatment	Duration of Trial	Number Needed to Treat (95% CI)	Final Quality of Evidence Based on GRADE
Pregabalin	4-13 weeks	7.7 (6.5-9.4)	High
Gabapentin	4-9 weeks	6.3 (5.0-8.4)	High
SNRI antidepressants	3-13 weeks	6.4 (5.2-8.4)	High
Tricyclic antidepressants	3-9 weeks	3.6 (3.0-4.4)	Moderate
Topical lidocaine	2-4 weeks	NA	Low
Topical capsaicin (8%)	12 weeks	10.6 (7.4-19)	High
Tramadol	4-9 weeks	4.7 (3.6-6.7)	Low moderate
Strong opioids	4-12 weeks	4.3 (3.4-5.8)	Low moderate

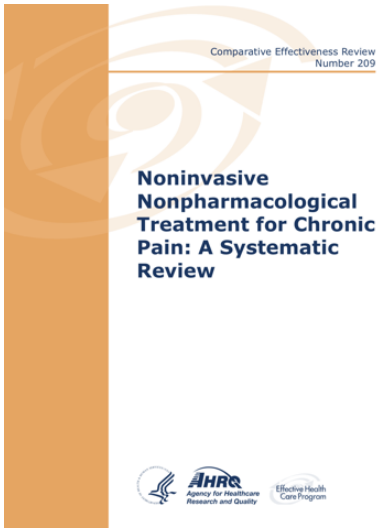
Attal N. and Bouhassira D. 2016

What about noninvasive and nonpharmacological treatments for chronic pain ?

Most effect small, but ”no harm”

Interventions that improved function and/or pain for at least 1 month when used for

- **Chronic low back pain:** Exercise, psychological therapies [CBT], spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, multidisciplinary rehabilitation (MDR).
- **Chronic neck pain:** Exercise, low-level laser, Alexander Technique, acupuncture.
- **Knee osteoarthritis:** Exercise, ultrasound.
- **Hip osteoarthritis**: Exercise, manual therapies.
- **Fibromyalgia:** Exercise, CBT, myofascial release massage, tai chi, qigong, acupuncture, MDR.
- **Chronic tension headache:** Spinal manipulation.



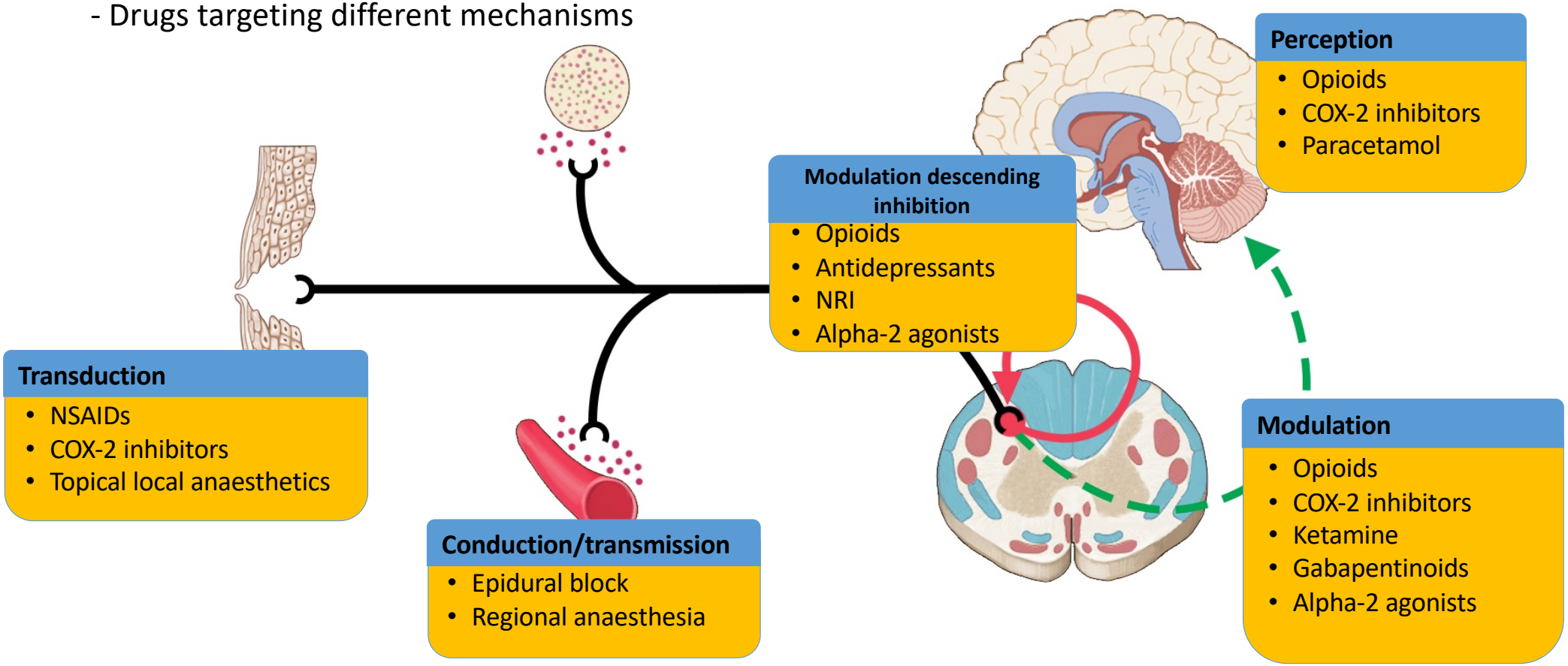
Most effects were small. Long-term evidence was sparse.

There was no evidence suggesting serious harms from any of the interventions studied; data on harms were limited.

Skelly AC et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. AHRQ Publication No 18-EHC013-EF.

Multimodal pharmacotherapy of pain:

- Targeting the basic nociceptive processes[1,2]
- Combination of different drugs and/or routes of administration[3,4]
- Drugs targeting different mechanisms



Adapted from 1. Kumar *et al. OA Anaesthetics*. 2014;2:2 and 2. Julius and Basbaum. *Nature*. 2001;413:203
3. Lee *et al. Best Pract & Res Clin Anaesth.* 2018;32:101e111; 4. Dunkman *et al. Surg Clin North Am.* 2018;98:1171

Combination Drug Therapy (CDT)

Types of drug combinations

- combination of drugs from the same drug class that differ in their pharmacokinetics
- combination of two or more drugs from different drug classes
- combination of drugs delivered through different routes
- fixed ratio combinations

Add-on therapy

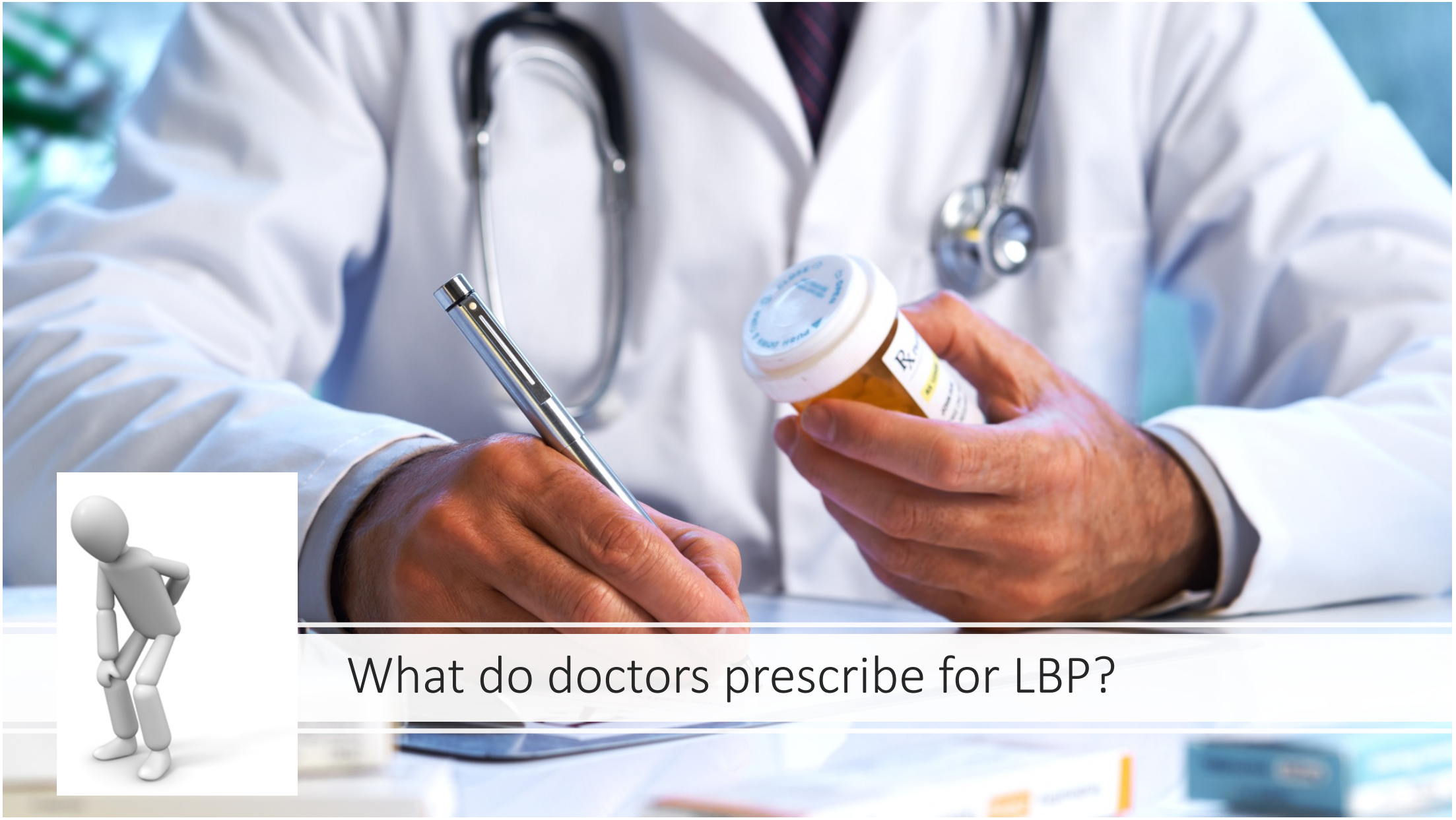
- refers to pharmacotherapy in which a selected medication is added to an existing treatment regimen

Mao, Gold & Backonja J. Pain 2011

Examples of Adverse Effects from Drug Combinations

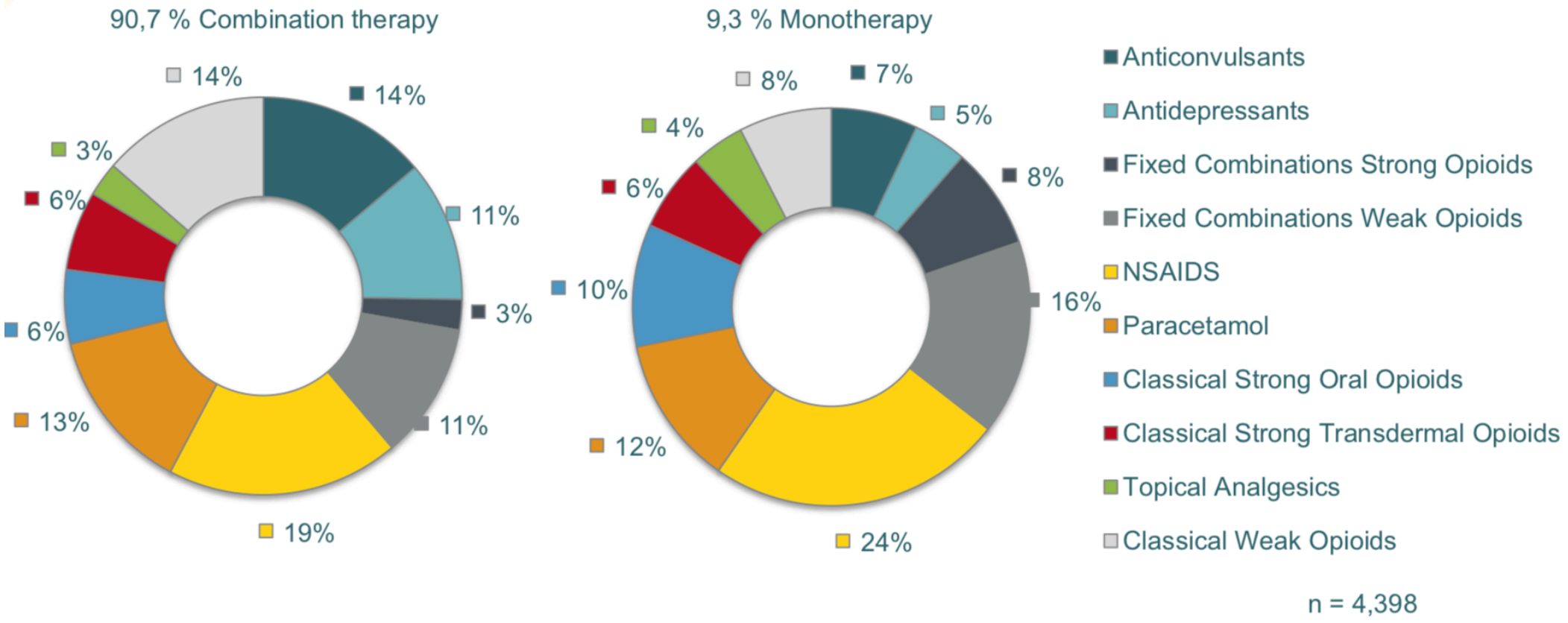
Serotonin Syndrome ***tramadol+TCA or SNRI***	**Sedation/Confusion** ***opioid+TCA or SNRI***	**Constipation** ***opioid+TCA or SNRI***
Liver Toxicity ***duloxitine+acetaminophen***	**Electrolyte Change** ***gabapentin+topiramate***	**Hematological Change** ***carbamezapine+mexiletine***
Endocrinological Change ***opioid analgesic***	**Addiction/Abuse** ***opioid analgesic***	**Common Side Effects** ***any drug combination***

Mao, Gold & Backonja J. Pain 2011



What do doctors prescribe for LBP?

Majority of health care professionals relies on combination therapies for treatment of severe chronic low back pain



https://www.change-pain.com/grt-change-pain-portal/change_pain_home/chronic_pain/physician/publications/physician_survey_results/en_EN/312500033.jsp

assessed 24 August 2019

CMRO

Current Medical Research & Opinion Vol. 27, No. 1, 2011, 11–33

0300-7995
doi:10.1185/03007995.2010.534446

Article FT-0105.R1/534446

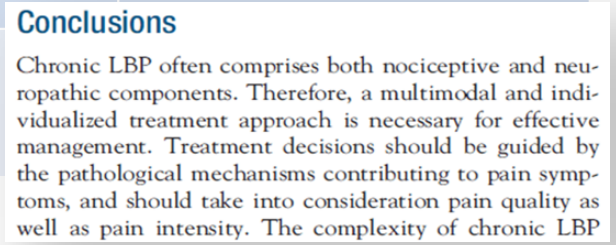
Review

Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components

Bart Morlion
University Hospitals Leuven, Leuven, Belgium

Morlion B. CMRO 2011, Vol 27, No. 1, 11-33

Drug class	Effective in nociceptive pain	Effective in neuropathic pain	Effective alone in neuropathic CLBP	Effective in combination in neuropathic CLBP
Paracetamol	✓	X	X	✓ with tramadol
NSAIDs	✓	X	X	✓ COX2 with pregabalin
Opioids	✓	✓	✓ for tapentadol Lack of adequate studies for other opioids in CLBP	✓ Buprenorphine with pregabalin
Antidepressants	X	✓	✓ for duloxetine No clear evidence/conflicting data[b]	
Anticonvulsants	X	✓	X	✓ With COX2 with opioids
Topical lidocaine/capsaicin	X	✓[a]	Lidocaine ✓ Capsaicin ✓	



Conclusions

Chronic LBP often comprises both nociceptive and neuropathic components. Therefore, a multimodal and individualized treatment approach is necessary for effective management. Treatment decisions should be guided by the pathological mechanisms contributing to pain symptoms, and should take into consideration pain quality as well as pain intensity. The complexity of chronic LBP

✓, effective; x, not effective.
a No label.
b Urquhart DM, Hoving JL, Assendelft WW, et al. Antidepressants for non-specific low back pain. Cochrane Database Syst Rev 2008:CD001703

Morlion B. CMRO 2011, Vol 27, No. 1, 11-33

Hindawi Publishing Corporation
Pain Research and Treatment
Volume 2012, Article ID 154781, 8 pages
doi:10.1155/2012/154781

Review Article

Antineuropathic and Antinociceptive Drugs Combination in Patients with Chronic Low Back Pain: A Systematic Review

Carlo Luca Romanò,[1] Delia Romanò,[1] and Marco Lacerenza[2]

[1] *Centro di Chirurgia Ricostruttiva, Istituto Ortopedico I.R.C.C.S. Galeazzi, Via R. Galeazzi 4, 20161 Milano, Italy*
[2] *Centro di Medicina del Dolore, Casa di cura S. Pio X, Fondazione Opera San Camillo, Via F. Nava 31, 20159 Milano, Italy*

- a rational approach would be targeting the different mechanisms of pain by combining specific drug agents
- ,… remarkably few clinical trials are currently available to validate this hypothesis.
- different reasons:
  - the difficulty in designing/performing clinical trials involving more treatments at the same time;
  - potential drugs' interactions and possible adverse effects. unpredictable dosing regimen.
  - scarce economical interest of drug companies.

Romano CL et al. Pain Research and Treatment, Volume 2012,

J Orthopaed Traumatol (2009) 10:185–191
DOI 10.1007/s10195-009-0077-z

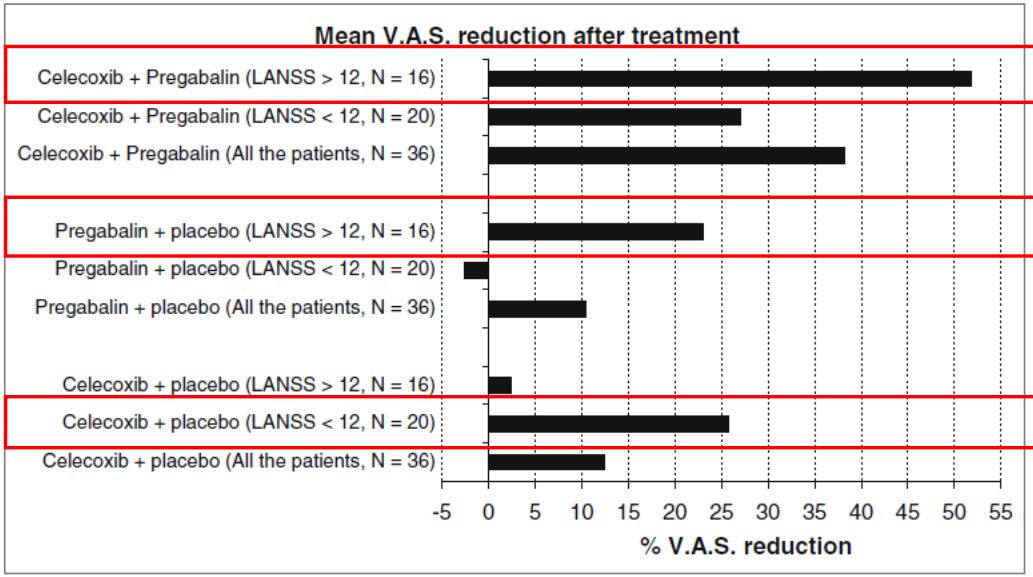
ORIGINAL ARTICLE

Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain

Carlo Luca Romanò · Delia Romanò · Cristina Bonora · Giuseppe Mineo

Prospective randomized trial,
36 patients received three consecutive 4-week treatments, randomly assigned.

LANSS ≥12 neuropathic pain
LANSS <12 nociceptive pain



mixed pain

neuropathic pain

nociceptive pain

p= 0.0001

Romano CL et al. J Orthopaed Traumatol (2009) 10:185-191

Pain Medicine, 0(0), 2019, 1–16
doi: 10.1093/pm/pnz216
Review Article

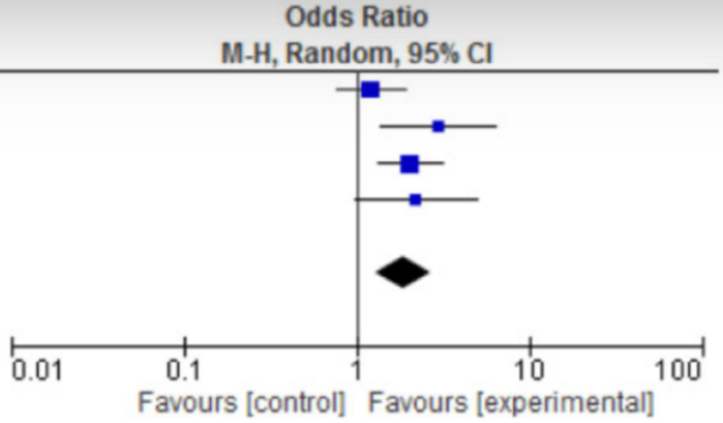
Effect of Combined Diclofenac and B Vitamins (Thiamine, Pyridoxine, and Cyanocobalamin) for Low Back Pain Management: Systematic Review and Meta-analysis

Carlos-Alberto Calderon-Ospina , MD, MSc, PhD,*,[a] Mauricio Orlando Nava-Mesa, MD, MSc, PhD,[†,a] and Carlos Emilio Arbeláez Ariza, MD, MSc[‡]

…combination therapy of diclofenac with TPC might have an analgesic superiority compared with diclofenac monotherapy in acute LBP. However, there is not enough evidence to recommend this therapy in other types of pain due to the scarcity of high-quality studies.

	Experimental		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Brüggemann 1990	53	184	48	192	32.4%	1.21 [0.77, 1.92]
Kuhlwein 1990	30	61	15	61	17.2%	2.97 [1.38, 6.40]
Mibielli 2009	87	187	55	185	34.5%	2.06 [1.34, 3.15]
Vetter 1988	19	116	10	122	15.9%	2.19 [0.97, 4.94]
Total (95% CI)		**548**		**560**	**100.0%**	**1.87 [1.28, 2.72]**
Total events	189		128			

Heterogeneity: Tau² = 0.06; Chi² = 5.09, df = 3 (P = 0.17); I² = 41%
Test for overall effect: Z = 3.25 (P = 0.001)



Clinical and Experimental Rheumatology 2017

The role of centralised pain in osteoarthritis

D.J. Clauw[1], A.L. Hassett[2]

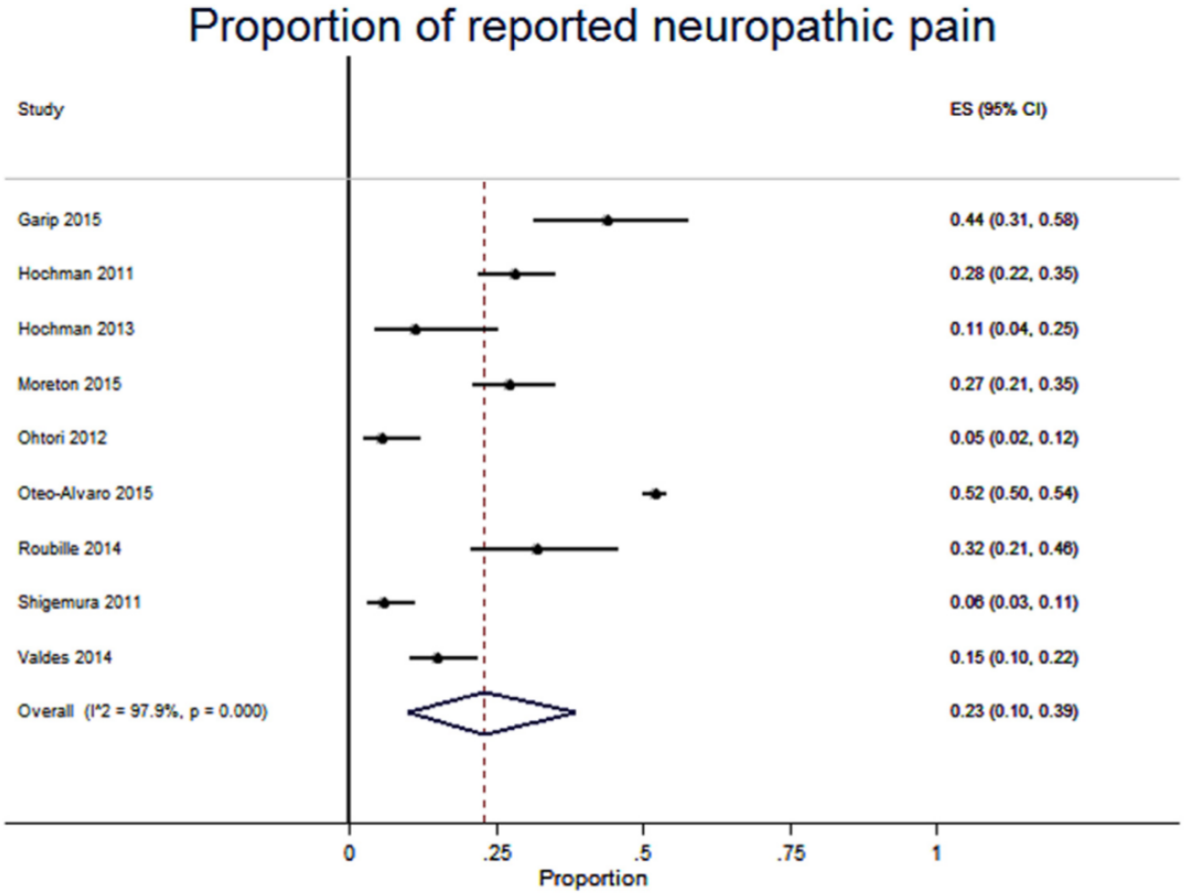
While osteoarthritis is generally considered a peripherally mediated pain state, a subset of these patients also manifests centrally driven pain characteristics.

Thus, osteoarthritis can also be thought of as a "mixed" pain state and this requires a more tailored approach to treatment.

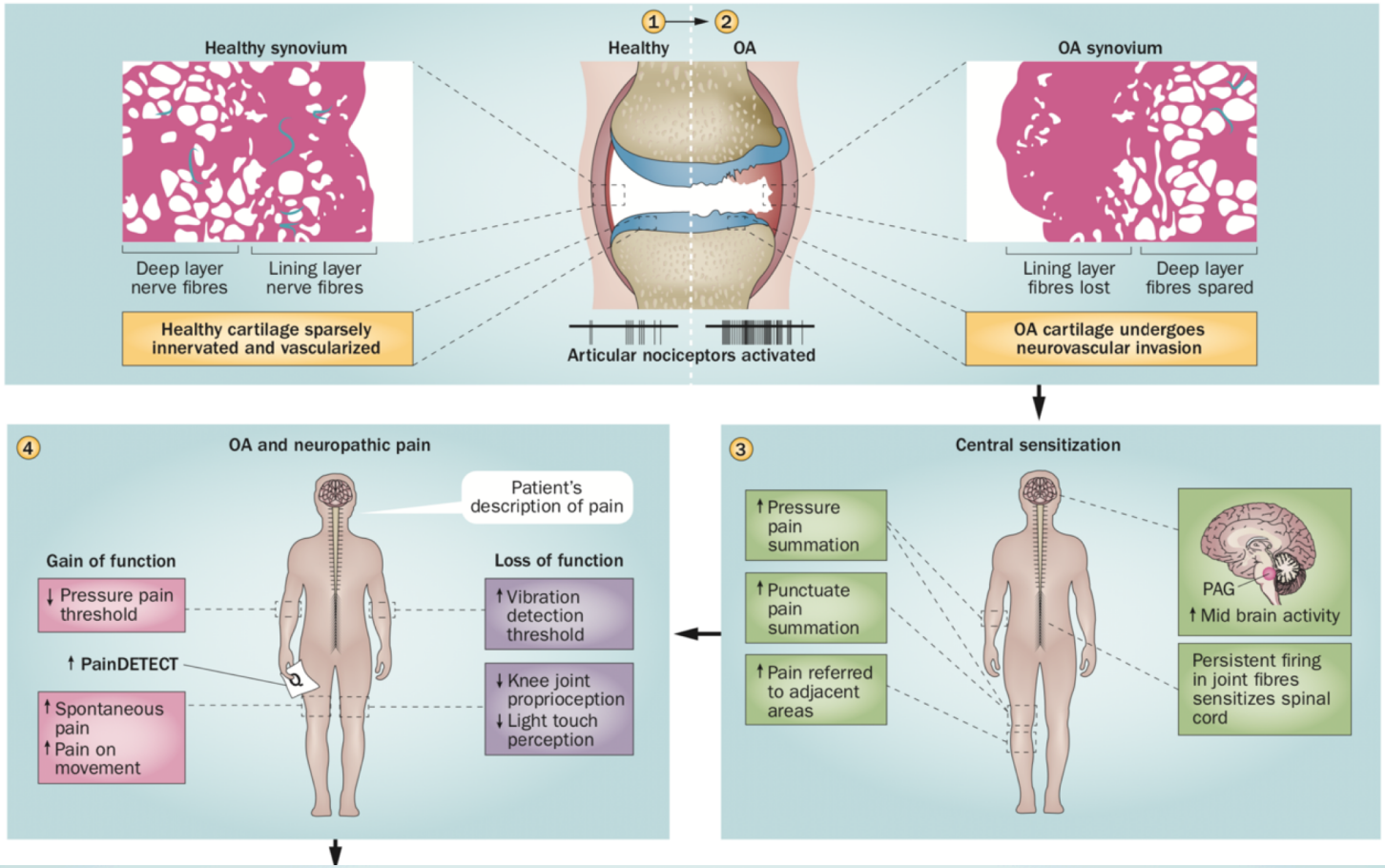
By carefully assembling clues from a history and physical examination, clinicians can now begin to identify the sub-sets of individuals with what were once considered purely "peripheral" pain syndromes, and treat these patients with more centrally- than peripherally- directed pharmacological and non- pharmacological approaches.

Clauw DJ and Hassett Clin Exp Rheumatol. 2017

Knee osteoarthritis: Prevalence estimates for neuropathic pain



H.P. French et al. / Seminars in Arthritis and Rheumatism 47 (2017) 1–8



Tailor treatment to neuropathic pain

- Tricyclic antidepressants and SNRIs
- Gabapentinoids
- Dual-action therapy e.g. Tapentadol
- Combination therapy e.g. Gabapentinoids + NSAID

Thakur, M. et al. Nat. Rev. Rheumatol. 10, 374–380 (2014)

Original Article | http://dx.doi.org/10.3349/ymj.2013.54.5.1253
pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 54(5):1253-1258, 2013 | YMJ

Efficacy of Combination of Meloxicam and Pregabalin for Pain in Knee Osteoarthritis

Seiji Ohtori, Gen Inoue, Sumihisa Orita, Masashi Takaso, Yawara Eguchi, N
Shunji Kishida, Kazuki Kuniyoshi, Yasuchika Aoki, Tetsuhiro Ishikawa, Ma
Hiroto Kamoda, Miyako Suzkuki, Junichi Nakamura, Gou Kubota, Yoshihiro Sakuma, Yasuhiro Oikawa,
Tomoaki Toyone, Kazuhide Inage, Takeshi Sainoh, Kazuyo Yamauchi, and Kazuhisa Takahashi

Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan.

Literature:
Mixed pain in 20-35% of all OA cases

In this study 24,5% (painDETECT)

Ohtori S. et al. Yonsei Med J 54(5):1253-1258, 2013

	Mean±SEM			*p* value
	Meloxicam	Pregabalin	Meloxicam+pregabalin	
Pain score, visual analogue scale				
1 wk	4.6±2.4*	4.4±2.1†	3.4±2.0‡	0.023*,‡ 0.02†,‡
2 wks	3.6±2.0*	3.5±1.9†	2.2±1.7‡	.04*,‡
4 wks	2.0±2.1*	2.0±2.2†	1.0±1.2‡	
WOMAC score (4 wks)				
Pain	6.3±2.3*	6.6±3.0†	3.6±1.7‡	.045
Stiffness	4.9±2.5*	4.5±2.2†	2.5±1.2‡	0.03*,‡ 0.025†,‡
Physical function	30.0±10.0*	29.3±11.4†	18.3±8.4‡	0.025*,‡ 0.03†,‡
Total	41.2±10.5*	40.4±9.3†	24.4±7.2‡	0.02*,‡ 0.04†,‡

There was significant difference in all scores in the meloxicam+pregabalin group compared with the meloxicam or pregabalin only groups.
*,‡$p<0.05$.
†,‡$p<0.05$.
No significant difference in all scores was seen in the meloxicam only group compared with the pregabalin only group (*,†$p>0.05$).

Meloxicam + Pregabalin combination was statistically more effective compared with each drug alone.

Ohtori S. et al. Yonsei Med J 54(5):1253-1258, 2013

European Journal of Cancer 105 (2018) 79–87

Available online at www.sciencedirect.com

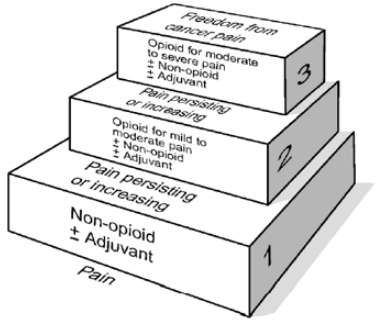
ScienceDirect

journal homepage: www.ejcancer.com

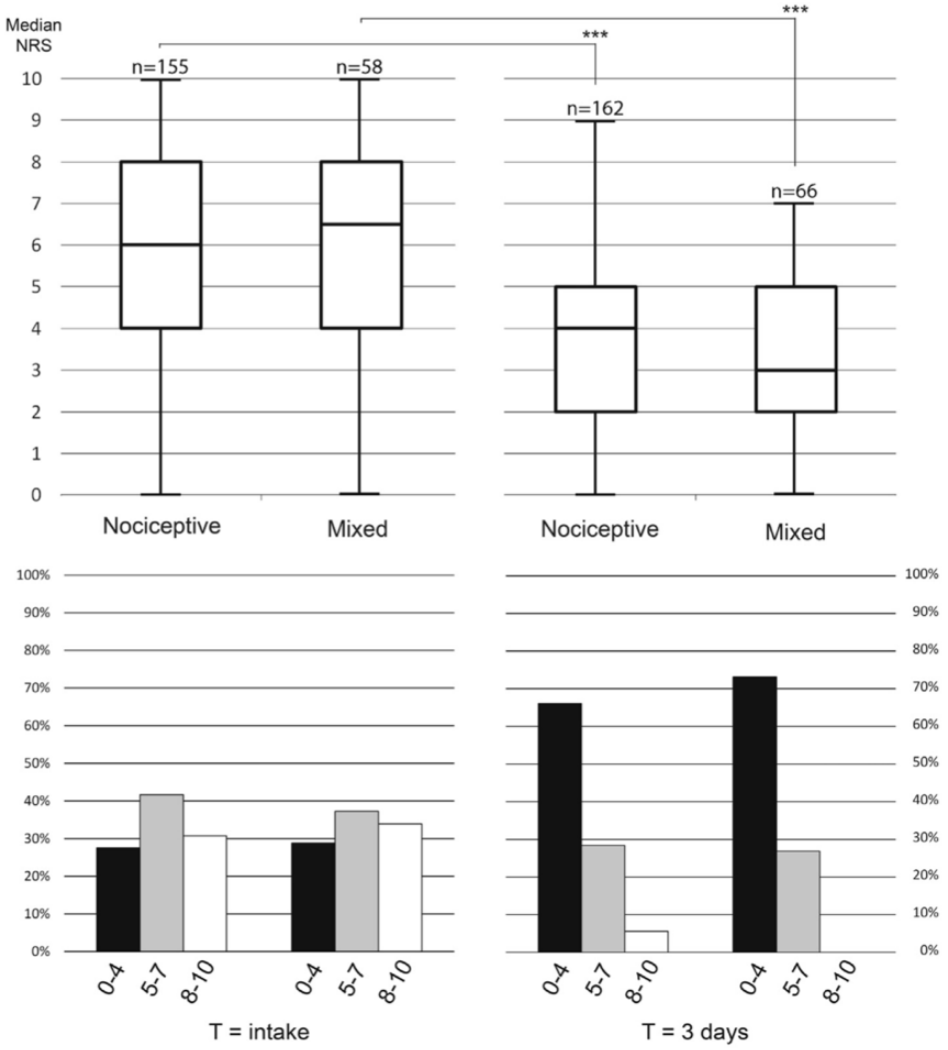
Original Research

Opioid responsiveness of nociceptive versus mixed pain in clinical cancer patients

Malik Bechakra [a,1], Floor Moerdijk [a,1], Joost van Rosmalen [b], Birgit C.P. Koch [c], Carin C.D. van der Rijt [d,e], Peter A.E. Sillevis Smitt [a], Joost L.M. Jongen [a,*]



Cancer pain relief. Geneva: World Health Organisation. 1986.



Bechakra M. et al. Eur J Cancer 105 (2018) 79-87

Proportions of opioids, MED and adjuvant analgesic medication

	Median (IQR) or n (%)			*p*-value
	Nociceptive and mixed pain	Nociceptive pain	Mixed pain	
Number of patients	240	173 (72.1)	67 (27.9)	
Type of opioid (T= 3d)				
Fentanyl			9.7)	*0.003*
Oxycodone			5.4)	0.057
Hydromorphone			.4)	*0.007*
Morphine			5)	0.689
Buprenorphine			0)	0.549
RMED			(0.74–3.00)	0.963
MED (T= 0d)			20–80)	0.987
MED (T= 3d)			20–100)	0.587
PFent (T= 3d)			(0.57–4.04) (n = 34)	0.465
Adjuvant analgesic medication (T=3d)				
Paracetamol	227 (94.6)	164 (94.8)	63 (94.0)	0.842
NSAIDs/coxibs	142 (59.2)	104 (60.1)	38 (56.7)	0.617
Anticonvulsants	73 (30.4)	36 (20.8)	37 (55.2)	*0.000*
Antidepressants	30 (12.5)	17 (9.8)	13 (19.4)	0.046
Ketamine	21 (8.8)	10 (5.8)	11 (16.4)	*0.009*

for the relief of cancer pain [27]. We therefore conclude that similar pain reductions and similar opioid requirements in both nociceptive and mixed cancer pain patients may be explained by similar opioid responsiveness in both groups and not by an increased prevalence of anticonvulsant or ketamine use in the mixed cancer pain group.

MED = morphine equianalgesic dose

Bechakra M. et al. Eur J Cancer 105 (2018) 79-87

European Journal of Cancer 105 (2018) 79–87

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Opioid responsiveness of nociceptive versus mixed pain in clinical cancer patients

Malik Bechakra [a,1], Floor Moerdijk [a,1], Joost van Rosmalen [b], Birgit C.P. Koch [c], Carin C.D. van der Rijt [d,e], Peter A.E. Sillevis Smitt [a], Joost L.M. Jongen [a,*]

5. Conclusion

We suggest that mixed cancer pain may be considered a type of nociceptive pain that should be treated primarily with opioids and that adjuvant analgesics or ketamine may only be added in case of insufficient analgesia or unacceptable side-effects from opioids.

Bechakra M. et al. Eur J Cancer 105 (2018) 79-87

Mixed Pain in Clinical Guidelines?

MEDECINS SANS FRONTIERES
← Return to Medical Guidelines

CLINICAL GUIDELINES
Diagnosis and treatment manual
GUIDE CLINIQUE ET THÉRAPEUTIQUE
Clinical guidelines

Version English

Authors/Contributors
Preface
Abbreviations and acronyms
Chapter 1: A few symptoms and syndromes
Shock
Seizures
Hypoglycaemia

			monitor the child.
Level 3	**morphine**	possible	The child may develop withdrawal symptoms, respiratory depression and drowsiness when the mother receives morphine at the end of the third trimester and during breast-feeding. Administer with caution, for a short period, at the lowest effective dose, and monitor the child.

Neuropathic pain

Commonly used analgesics are often ineffective in treating this type of pain.

Treatment of neuropathic pain is based on a combination of two centrally acting drugs:

amitriptyline PO
Adults: 25 mg once daily at bedtime (Week 1); 50 mg once daily at bedtime (Week 2); 75 mg once daily at bedtime (as of Week 3); max.150 mg daily.
Reduce the dose by half in elderly patients.

carbamazepine PO
Adults: 200 mg once daily at bedtime (Week 1); 200 mg 2 times daily (Week 2); 200 mg 3 times daily (as of Week 3)
Given its teratogenic risk, carbamazepine should only be used in women of childbearing age when covered by effective contraception (intrauterine device or injectable progestogen). It is not recommended in pregnant women.

Mixed pain

In mixed pain with a significant component of nociceptive pain, such as in cancer or AIDS, morphine is combined with antidepressants and antiepileptics.

Chronic pain

In contrast to acute pain, medical treatment alone is not always sufficient in controlling chronic pain. A multidisciplinary approach including medical treatment, physiotherapy, psychotherapy and nursing is often necessary to allow good pain relief and encourage patient selfmanagement.

Conclusion: One-fits all?

- Many chronic pain patients present with “Mixed Pain”
- The key question remains: sum of different types of pain or entity in its own right?
- Not defined in the IASP Terminology and not part of the new ICD 11
- No clear guidelines specific to mixed pain are currently available.
- Rational approach of mixed pain:
  - Personalized medicine
  - Multimodal management of chronic pain
  - Multimodal pharmacotherapy to manage the different types of pain.
    - More risk for adverse drug interactions

Thank you
for your attention !