OSTEORHEUMATOLOGY 2016

Genoa, October 20th – 21st

Physiopathology & Treatment Of Musculoskeletal Pain

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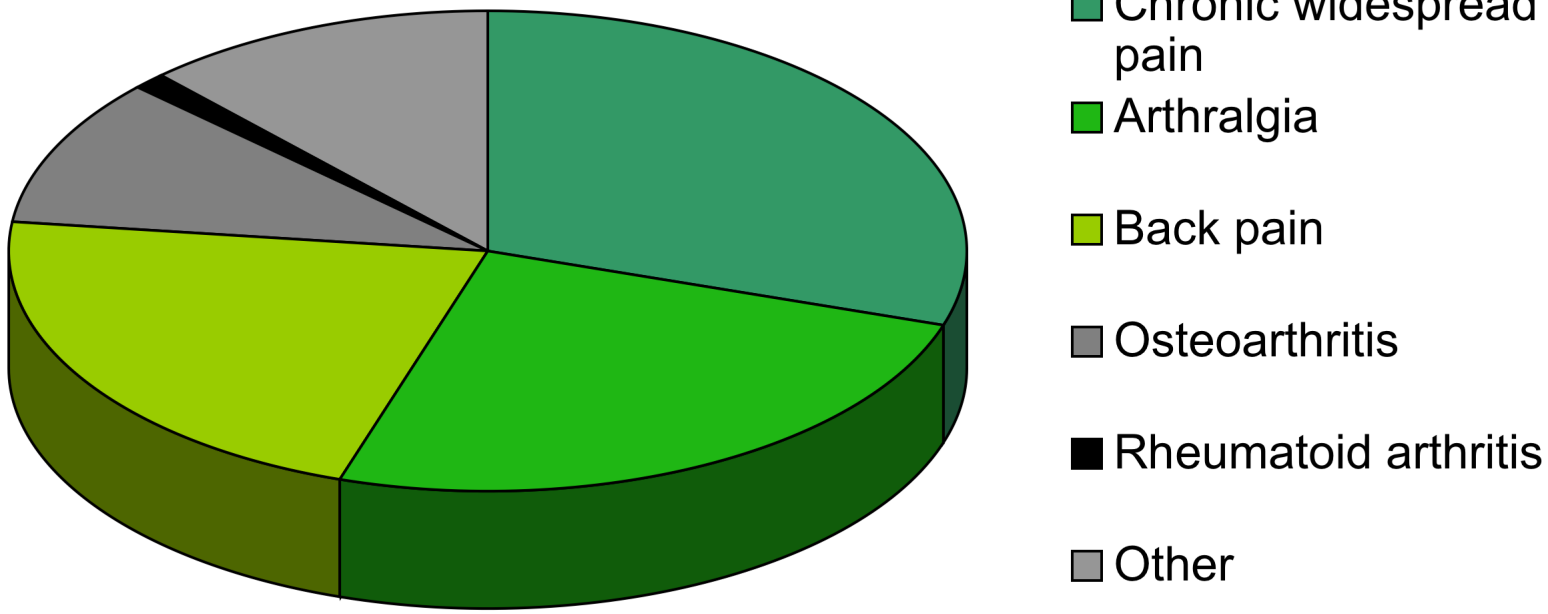
Epidemiology
Of Musculoskeletal Pain

New Musculoskeletal Consultations in UK (2001)



77% GP consultations for musculoskeletal pain

Parsons S et al., Medicine 2010

Musculoskeletal Pain: An Epidemic?

- **UK**: 46,5% of patients reported musculoskeletal pain in the last 3 months
- **Norway**: 85% of patients aged 20-72 yrs reported chronic musculoskeletal pain in the last year
- **Sweden**: 35% of patients reported chronic musculoskeletal pain lasting more than 3 months in the last year
- **Canada**: during years 1998-1999 the 25% of the population referred to a physician for chronic musculoskeletal pain

Elliott AM et al., Lancet 1999
Natvig B et al., Tidsskr Nor Laegeforen 1994
Bergman S et al., J Rheumatol 2001
Power JD et al., J Rheumatology 2006

Physiopathology Of Musculoskeletal Pain

Physiopathology Musculoskeletal Pain: Overview

- **Classical View**
  - to be peripheral in origin
  - induced by acute or chronic inflammation, or
  - morphostructural alterations in the involved joints
- **Sensitisation View**
  - based on the recognition of neurophysiological modifications in perception, transmission and processing of nociceptive afferents at the level of the CNS
  - permanent state of neuronal hyperexcitability involving all peripheral & central structures of nociceptive system

Cazzola M et al., Reumatismo 2014

Musculoskeletal Pain: Classical View Limitations

Discrepancy between:

1 – the intensity and characteristics of the pain reported by patients and the extent of the anatomical alterations detectable at the sites of the perceived pain (e.g., radiological grading of osteoarthritis);

2 – the inciting event and the presence of disproportionate spontaneous or stimulus-induced pain, allodynia and hyperalgesia (e.g., complex regional pain syndrome type I).

Bedson J et al., BMC Musculoskelet Disord 2008
Giusti A et al., RMD Open 2015

Musculoskeletal Pain & Radiological Alterations in Osteoarthritis

Proportion (%) of patients experiencing knee pain in populations with radiographic osteoarthritis (Kellgren & Lawrence Knee OA Grading Scale)

Reference	Age Range	% Pain	KL OA grade
Lachance L et al. 2001	40-53	35%	2+
Hart DJ et al., 1991	45-65	56%	2+
Davis MA et al., 1992	45-75	41%	2
		59%	3
Claessens AA et al., 1990	>45	20%	2+
Odding E et al., 1998	>55	30%	2
		59%	3
Williams DA et al., 2004	51-80	79%	2+

Mod. from Bedson J et al., BMC Musculoskelet Disord 2008

Peripheral & Central Sensitisation

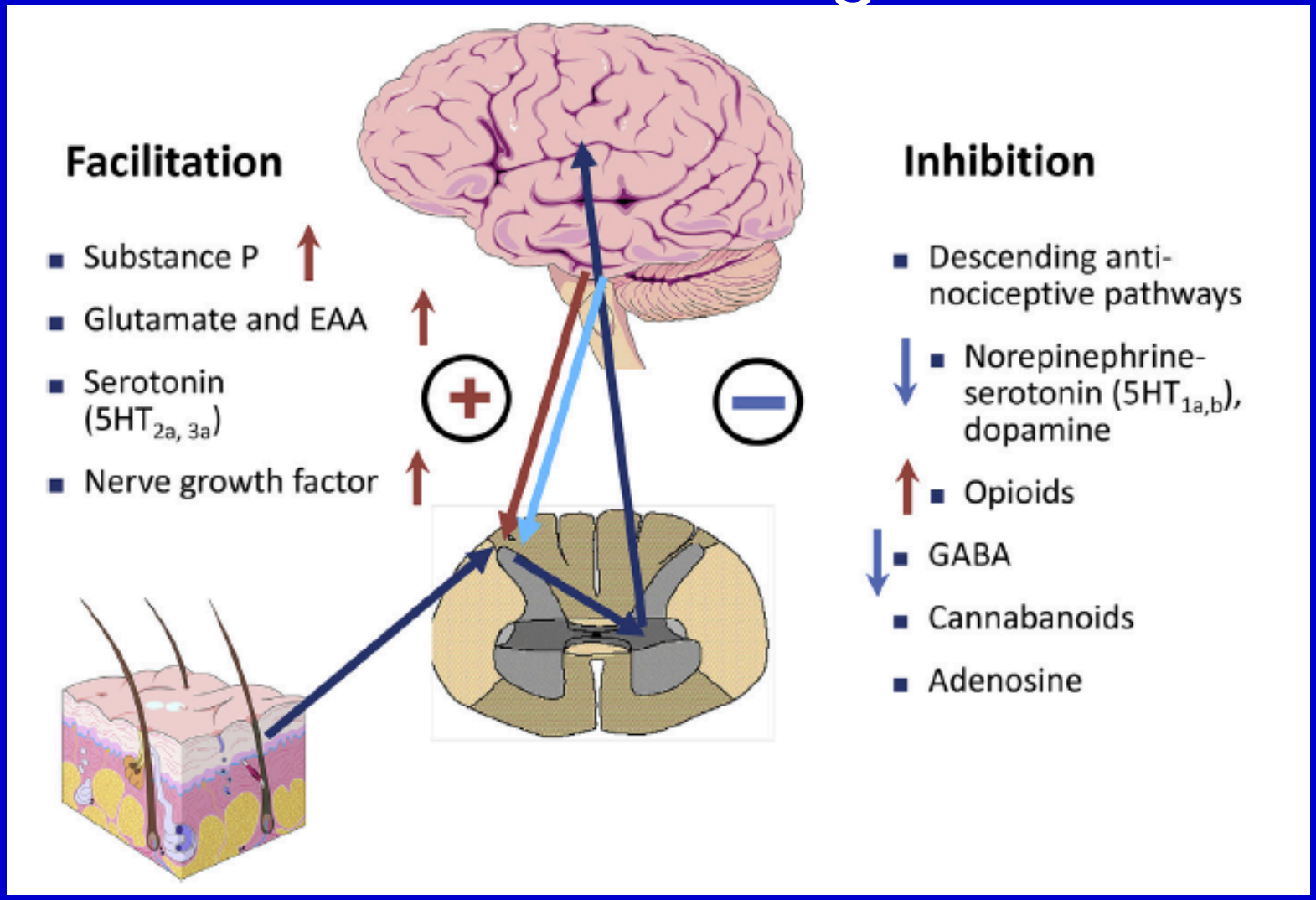
Peripheral

✓ Sensitivity of the peripheral endings of nociceptors modified by repeated mechanical, thermal stimuli or (inflammation) by variations in the chemical milieu;
✓ Sensitisation of primary afferent nociceptors associated with adrenergic supersensitivity;
✓ Aberrant cross-talk between sensory and sympathetic neurons in dorsal root ganglia;

Central

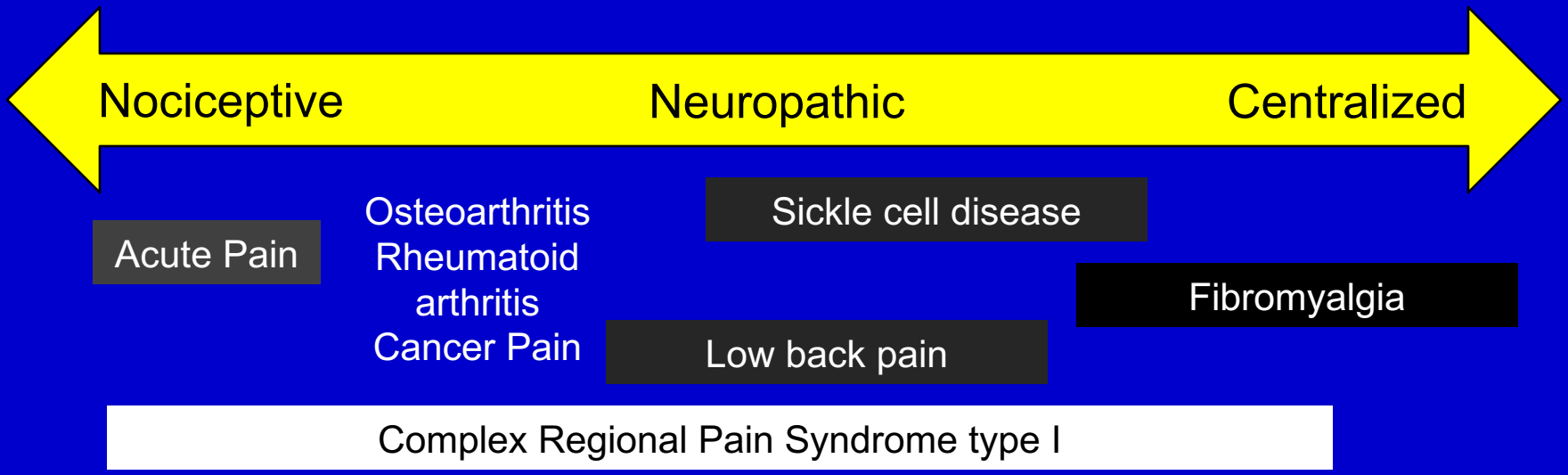
✓ State of neuronal hyperexcitability in response to peripheral stimuli that permanently modifies sensory processes (nociception);
✓ Sensitisation of nociception-specific or wide dynamic-range neurons in the dorsal horn;
✓ Descending nociceptive facilitation or impaired descending nociceptive inhibition.

CNS influences on Pain & Sensory Processing



Clauw DJ et al., Best Pract Res Clin Rheumatol 2015

Physiopathology Musculoskeletal Pain: The Pain Continuum



Pain related to tissue damage, due to trauma or inflammation

Pain related to damage of peripheral or central nerves

Pain resulting from persistent neuronal dysregulation, no nerve or tissue damage

Mod. from Arnold LM et al., Clin J Pain

Physiopathology Of Musculoskeletal Pain:

Osteoarthritis
CRPS type I
Bone Cancer

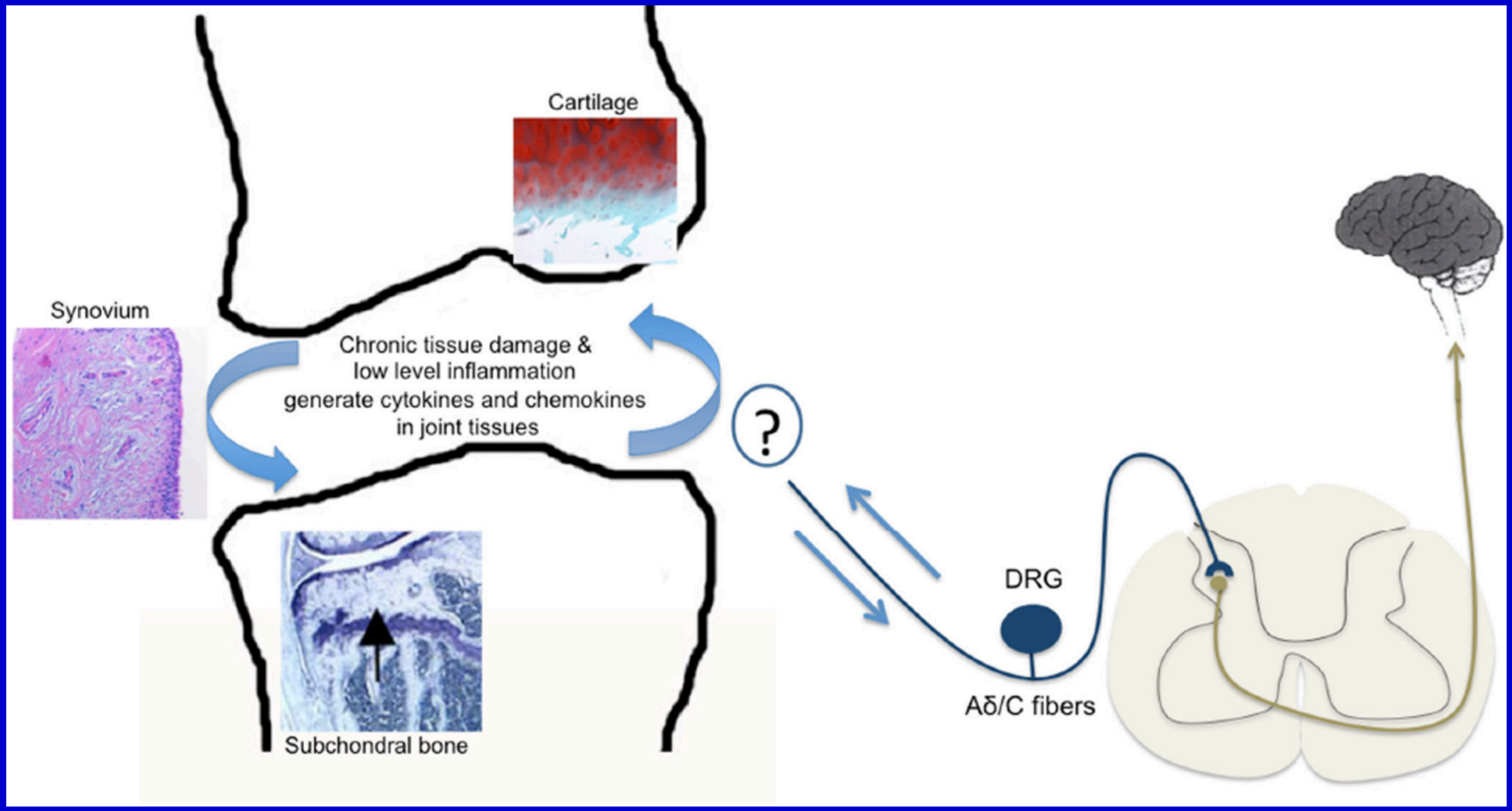
Physiopathology Of Musculoskeletal Pain:

Osteoarthritis

CRPS type I

Bone Cancer

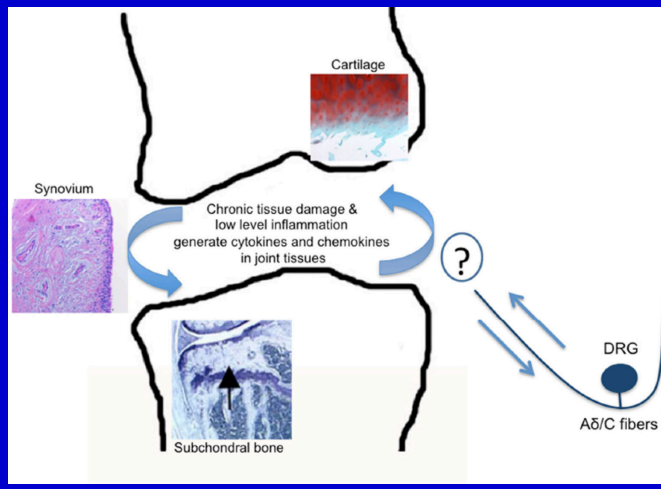
Peripheral Mechanisms of Osteoarthritis Pain

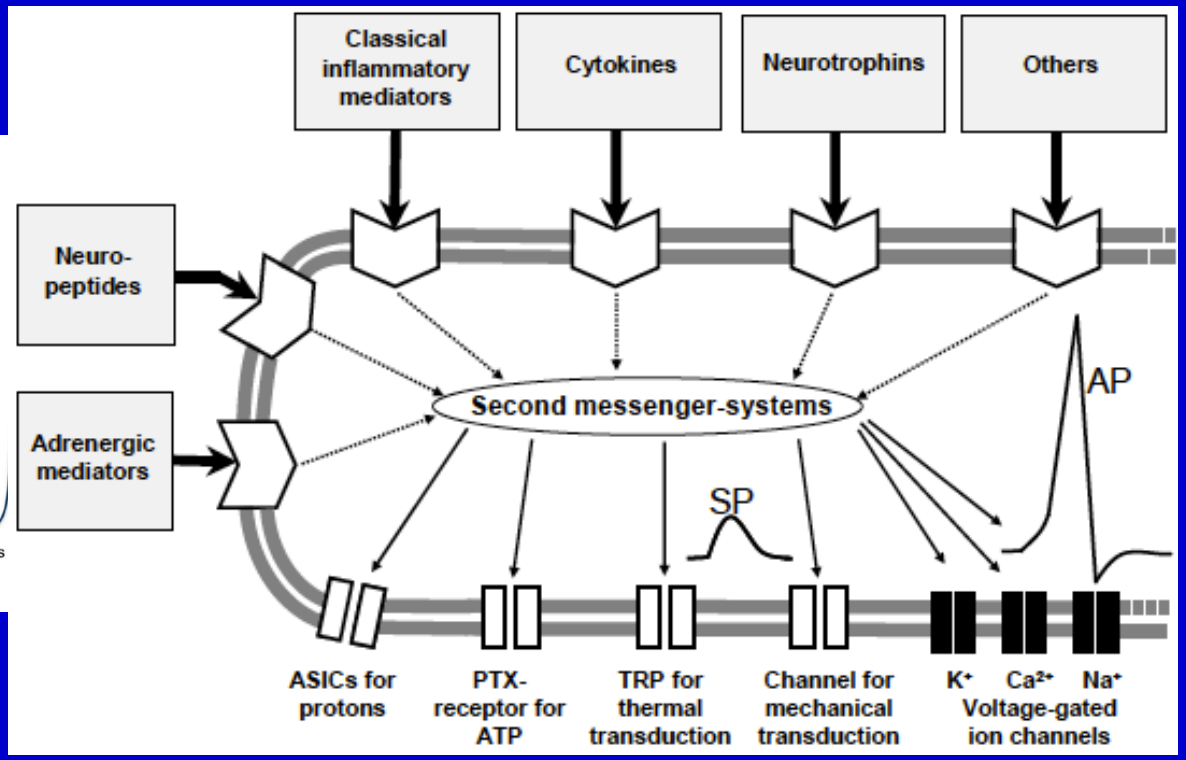


Nociceptors (medium-sized myelinated Aδ fibers and small unmyelinated C-fibers) detect noxious signals in the innervated tissues and carry them to the dorsal horn of the spinal cord.

Miller RE et al.,Cytokine 2014

Osteoarthritis Pain: Sensory Ending of a Nociceptor in the Tissue





The membrane displays receptors for mediators that act on different second messenger systems. Classical inflammatory mediators are bradykinin, prostaglandin E2, 5-hydroxytryptamine, and histamine.

Miller RE et al.,Cytokine 2014
Schaible HG et al., Arthritis Research & Therapy 2011

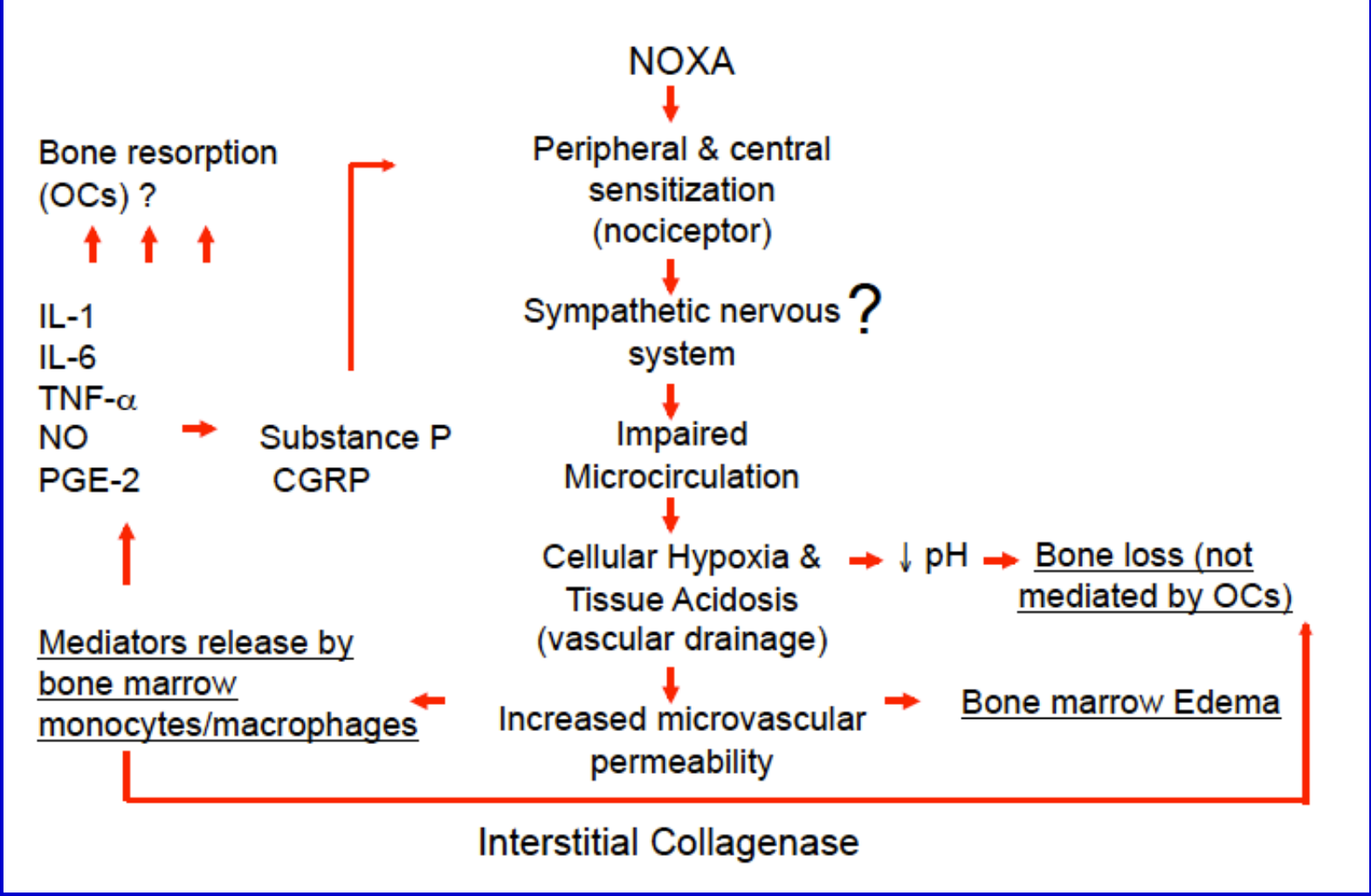
Physiopathology Of Musculoskeletal Pain:

Osteoarthritis

CRPS type I

Bone Cancer

Central & Peripheral Mechanisms in CRPS type I



Varenna M et al., CCMBM 2015
Giusti A et al., RMD Open 2015

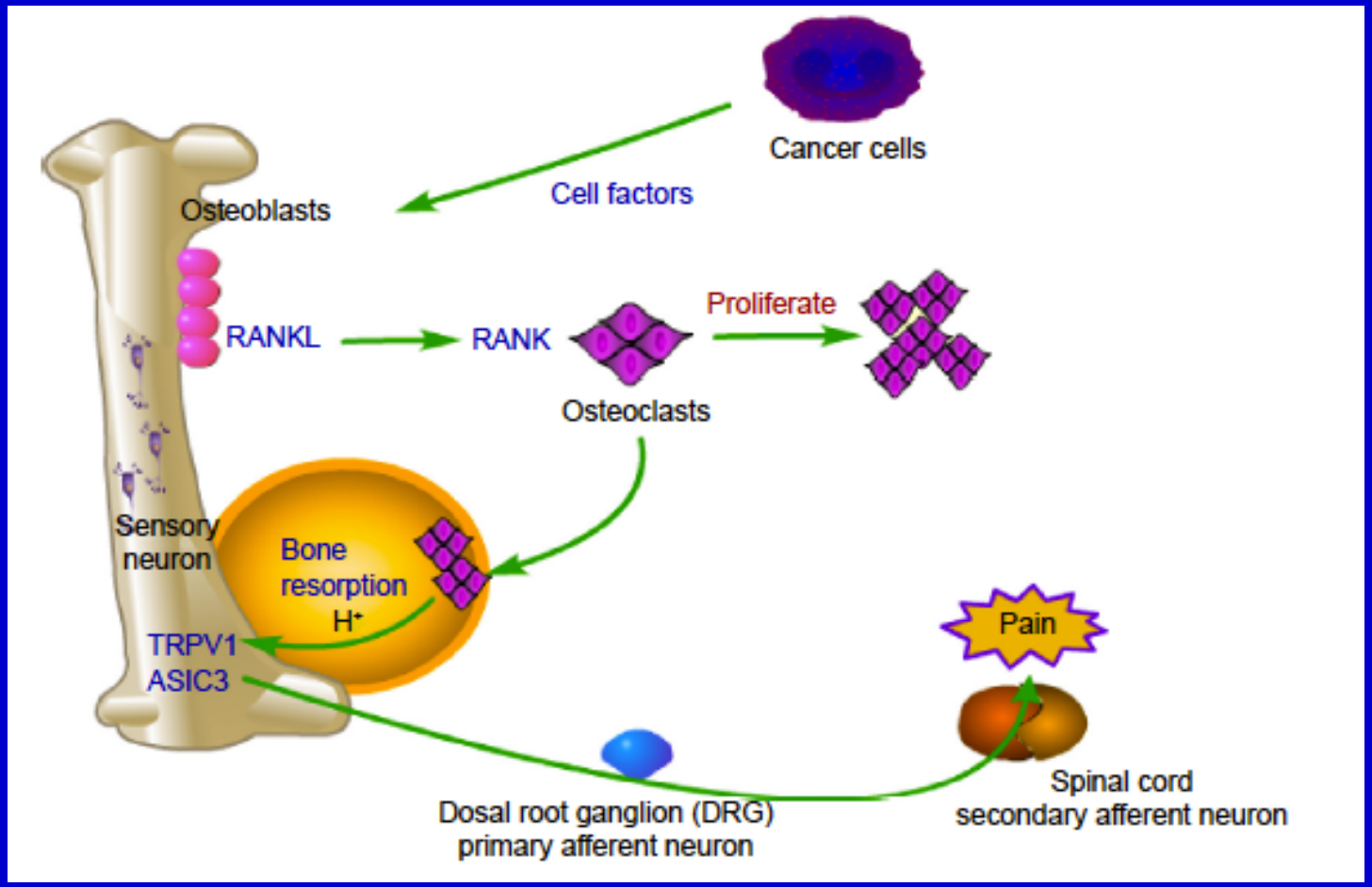
Physiopathology Of Musculoskeletal Pain:

Osteoarthritis

CRPS type I

Bone Cancer

Mechanism of Bone Cancer Pain

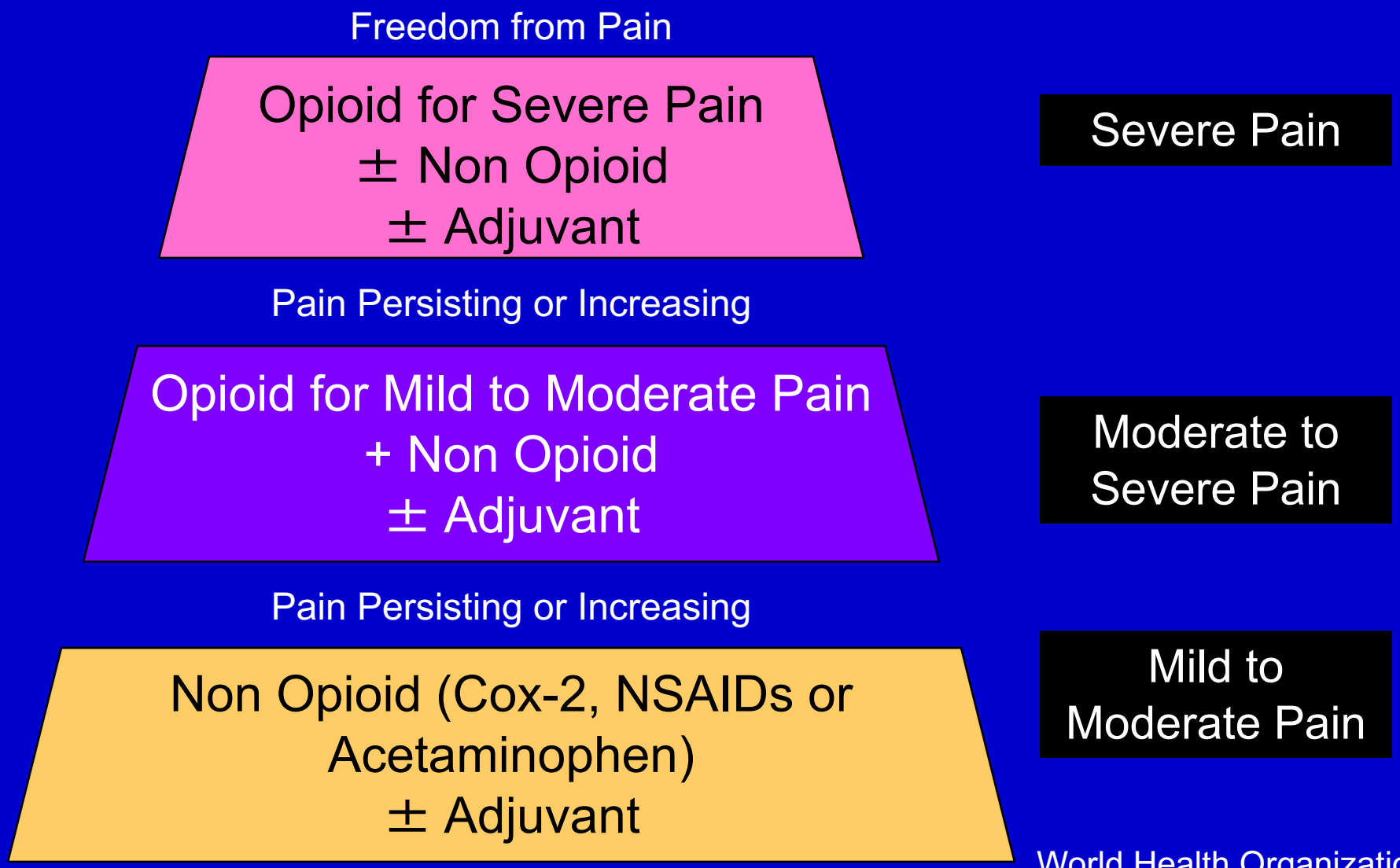


The acidic microenvironment directly excites sensory neurons innervating bone via activation of the acid-sensing nociceptors: TRPV1 (transient receptor potential vanilloid 1) and ASIC3 (acid-sensing ion channel 3).

Zhu XC et al., DDDT 2015

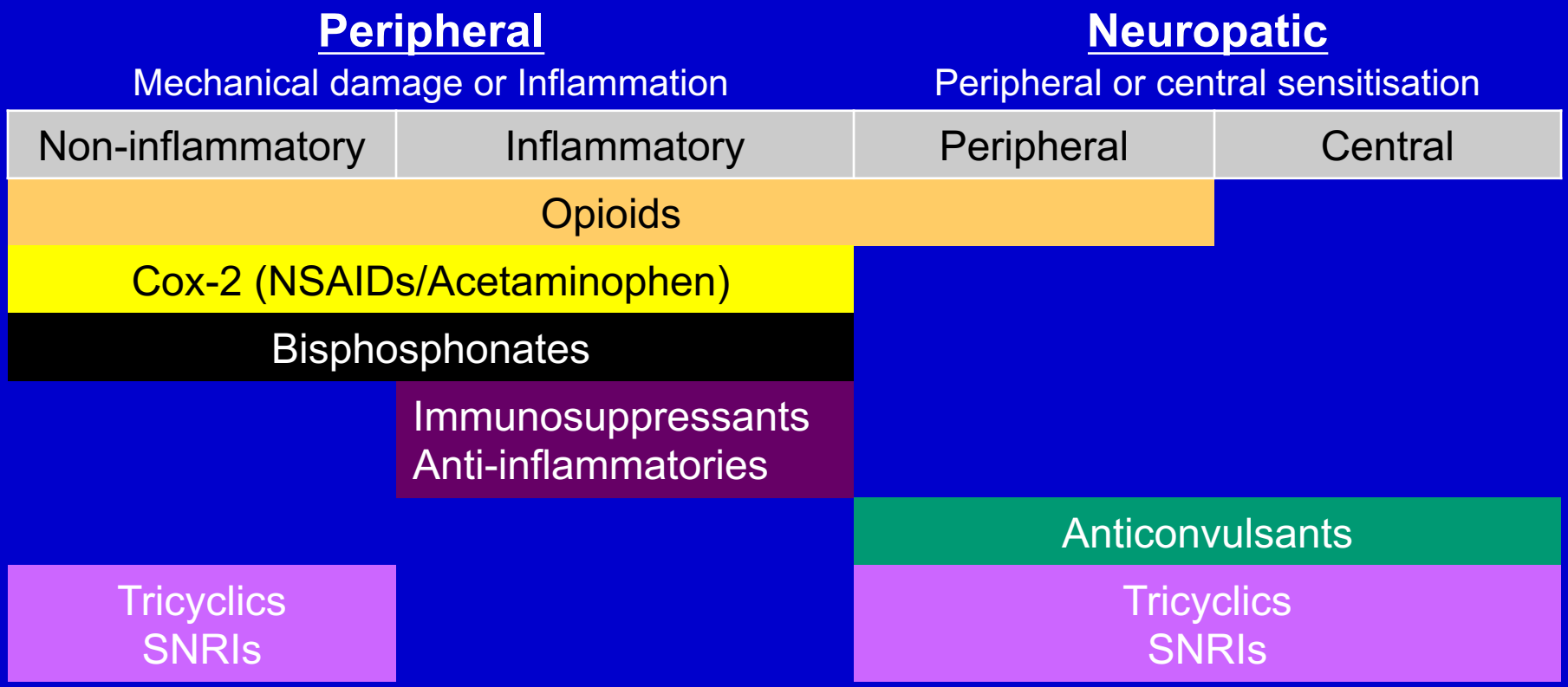
Treatment
Of Musculoskeletal Pain

Pain Treatment: Sequential Approach



World Health Organization

Physiopathology-based Treatment of Musculoskeletal Pain



Mod. from Clauw DJ et al., Best Pract Res Clin Rheumatol 2015

Treatment
Of Musculoskeletal Pain
NSAIDs or Acetaminophen

Acetaminophen is Less Effective Than NSAIDs

Fifteen RCTs involving 5986 participants:
Seven RCTs of acetaminophen versus placebo;
Ten RCTs of acetaminophen versus NSAIDs.

In the placebo-controlled RCTs, acetaminophen was superior to placebo in 5 out of 7 RCTs, with a similar safety profile.

THE COCHRANE COLLABORATION®

In the comparator-controlled RCTs, acetaminophen was less effective than NSAIDs. No significant difference was found overall between the safety of acetaminophen and NSAIDs.
Adverse GI events: 19% in the traditional NSAID group versus 13% in the acetaminophen group.

Towheed TE, et al., Cochrane Database Syst Rev 2006

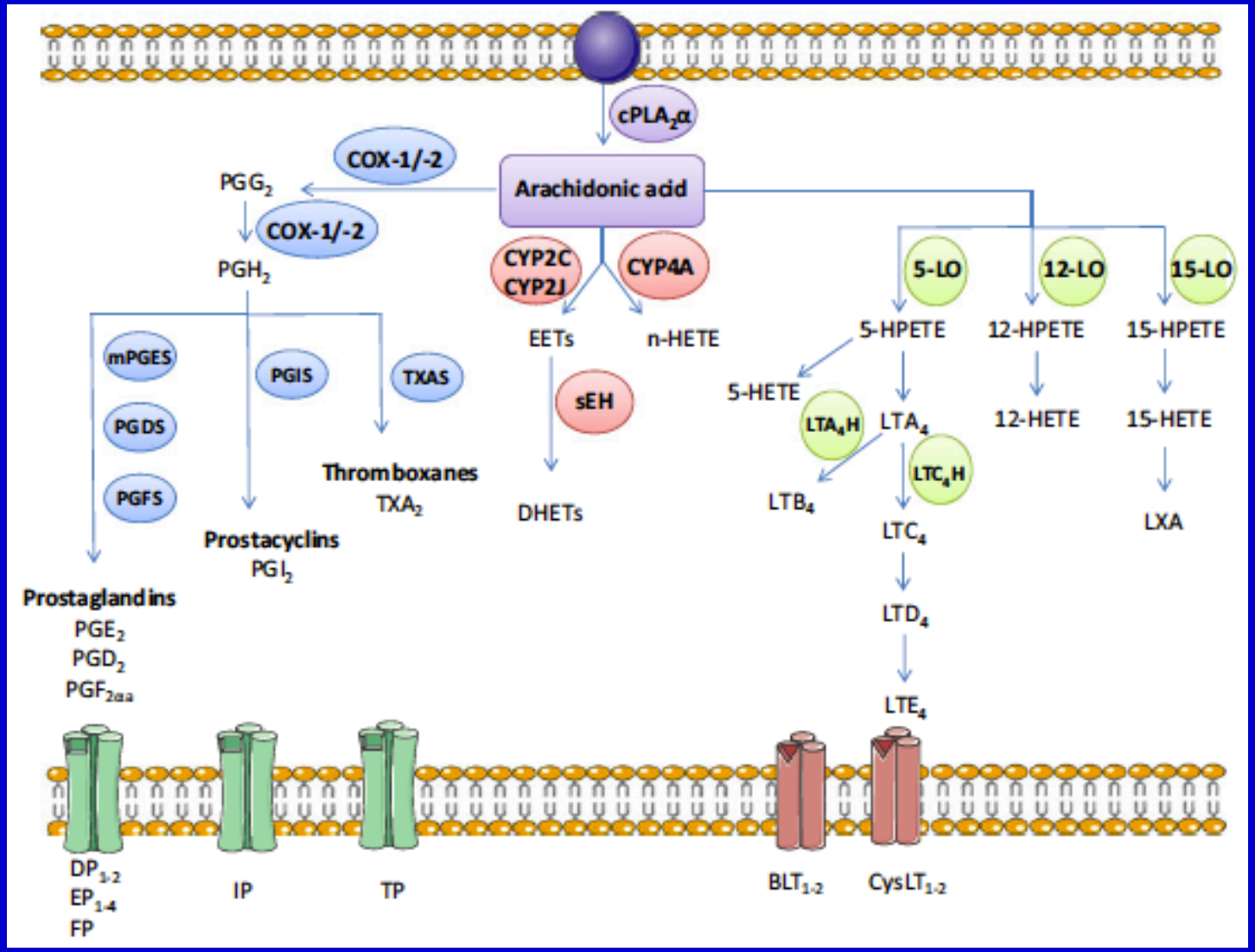
Non-Narcotic Analgesic Drugs & Risk of Incident Hypertension in US Women

	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	3365	551	636	716	
Cases	107	20	34	50	
Age-adjusted RR (95% CI)	1.0 (reference)	0.78 (0.47, 1.31)	1.42 (0.92, 2.20)	2.02 (1.38, 2.97)	<0.001
Multivariable* RR (95% CI)	1.0 (reference)	0.82 (0.48, 1.39)	1.33 (0.84, 2.08)	1.93 (1.30, 2.88)	<0.001
NSAIDs	0	1–100	101–400	> 400	*P* trend
Person years	3212	611	422	1024	
Cases	99	30	22	60	
Age-adjusted RR (95% CI)	1.0 (reference)	1.74 (1.09, 2.76)	1.48 (0.86, 2.51)	1.89 (1.31, 2.72)	0.003
Multivariable* RR (95% CI)	1.0 (reference)	1.72 (1.07, 2.78)	1.53 (0.89, 2.66)	1.78 (1.21, 2.61)	0.01
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	3127	827	808	506	
Cases	108	43	37	23	
Age-adjusted RR (95% CI)	1.0 (reference)	1.34 (0.91, 1.99)	1.11 (0.73, 1.70)	1.13 (0.68, 1.86)	0.71
Multivariable* RR (95% CI)	1.0 (reference)	1.28 (0.86, 1.92)	1.19 (0.77, 1.83)	1.12 (0.67, 1.86)	0.66

Forman JP et al., Hypertension 2005

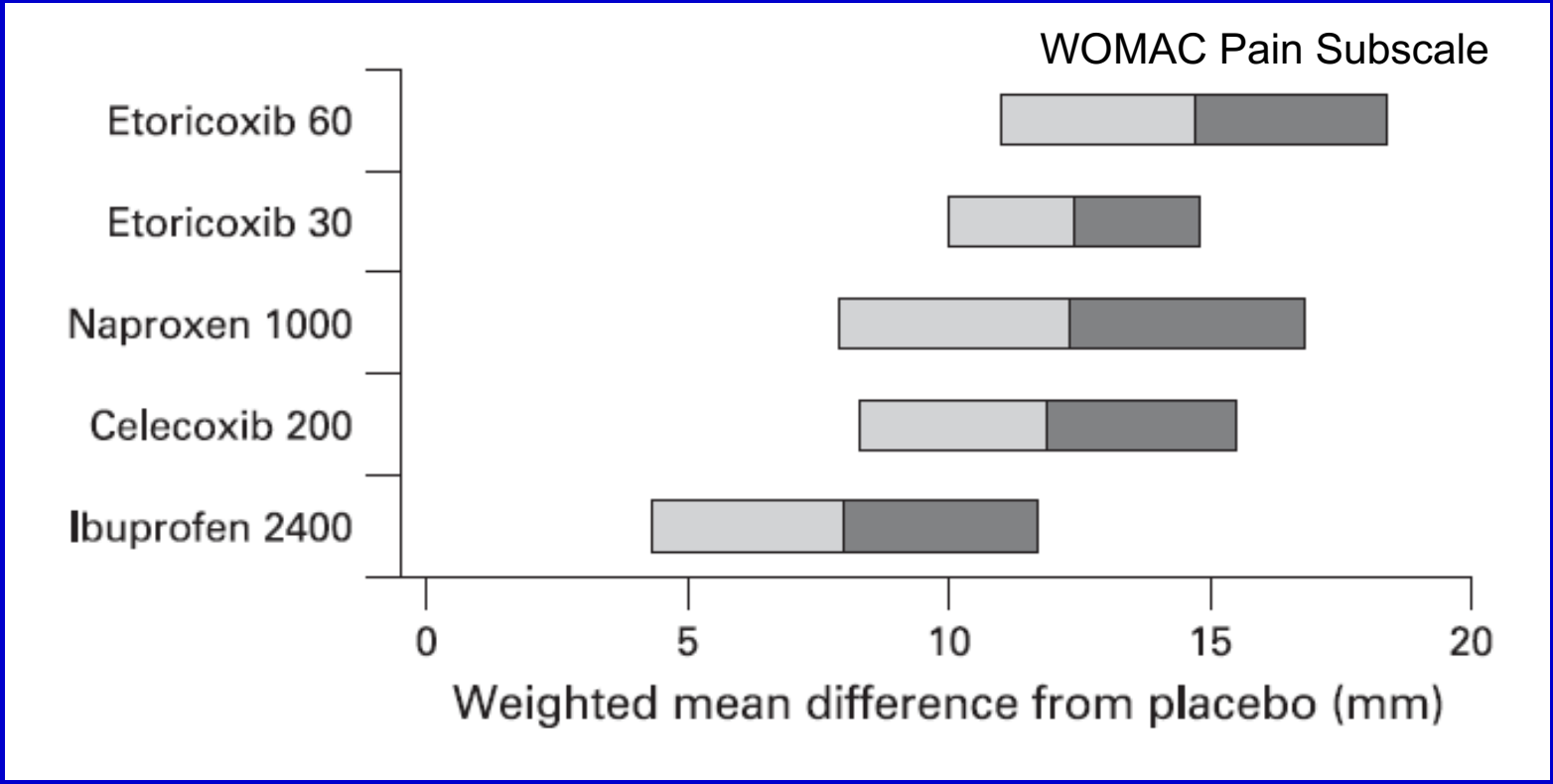
Treatment
Of Musculoskeletal Pain
NSAIDs or Cox-2

Modulators of Arachidonic Acid Cascade for Inflammation and Pain



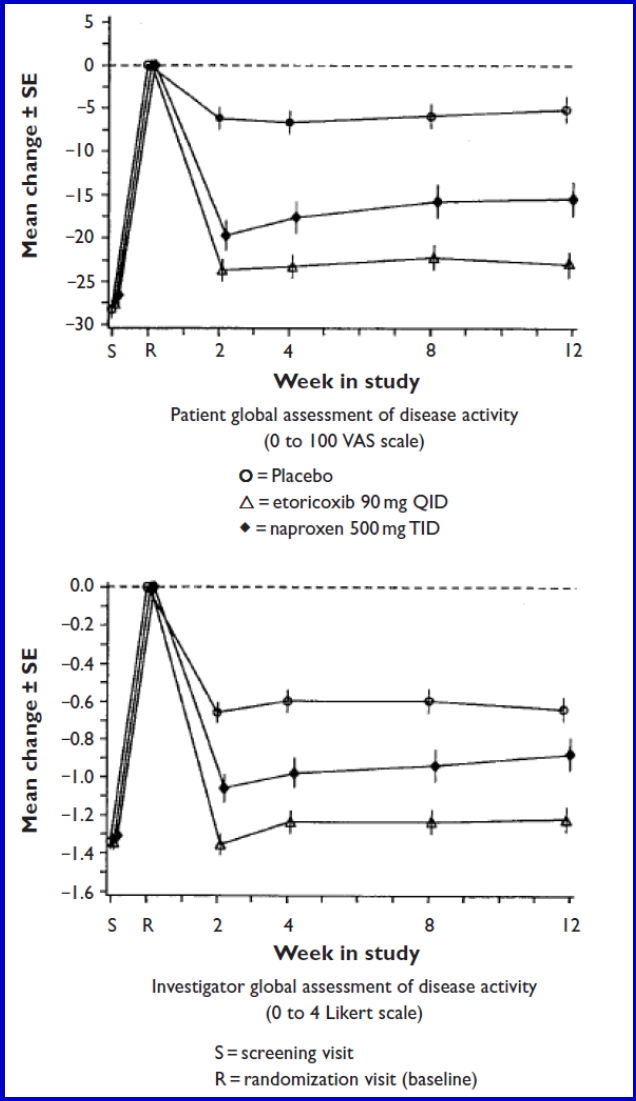
Cox-2 versus NSAIDs (highest dose) in Osteoarthritis

Seven RCTs (3554 patients) of etoricoxib in OA lasting >6 weeks



Moore RA et al. Ann Rheum Dis 2010

Cox-2 versus NSAIDs in Rheumatoid Arthritis



Global assessment results for etoricoxib versus placebo and naproxen in patients with rheumatoid arthritis.

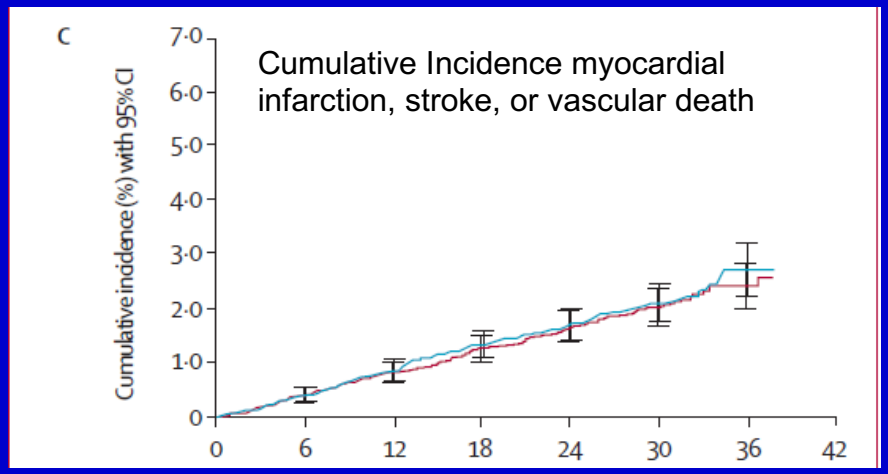
- Randomized, double-blind, controlled study;
- 816 adult patients with rheumatoid arthritis
- Randomized to receive etoricoxib 90 mg (n = 323), naproxen 500 mg BID (n = 170) or placebo (n = 323) for 12 weeks.

Etoricoxib demonstrated superior efficacy on all primary endpoints compared with naproxen ($p < 0.05$) or placebo ($p < 0.01$).

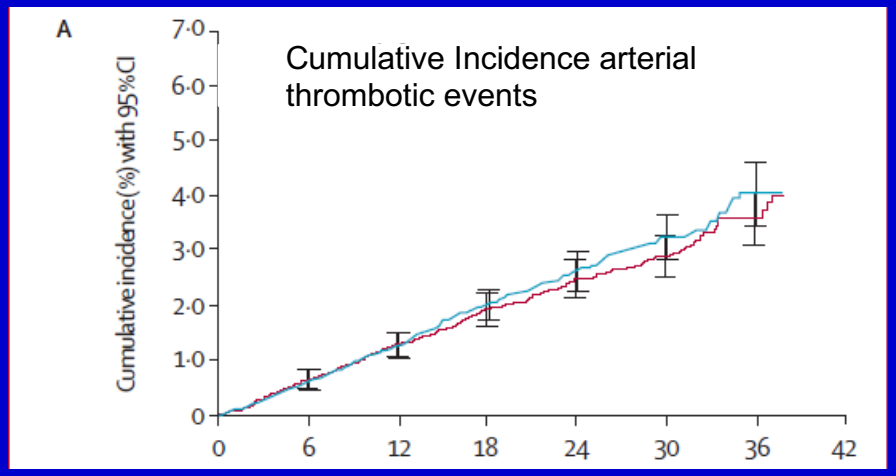
Efficacy was evident after 2 weeks and was maintained throughout the study period.

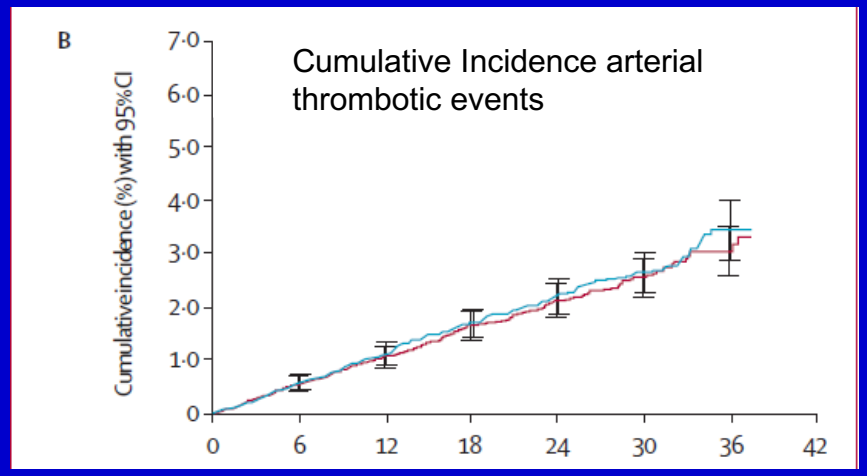
Matsumoto AK et al., J Rheumatol 2002

Cardiovascular Safety of Cox-2 versus NSAIDs (the MEDAL Study)



Diclofenac
Etoricoxib

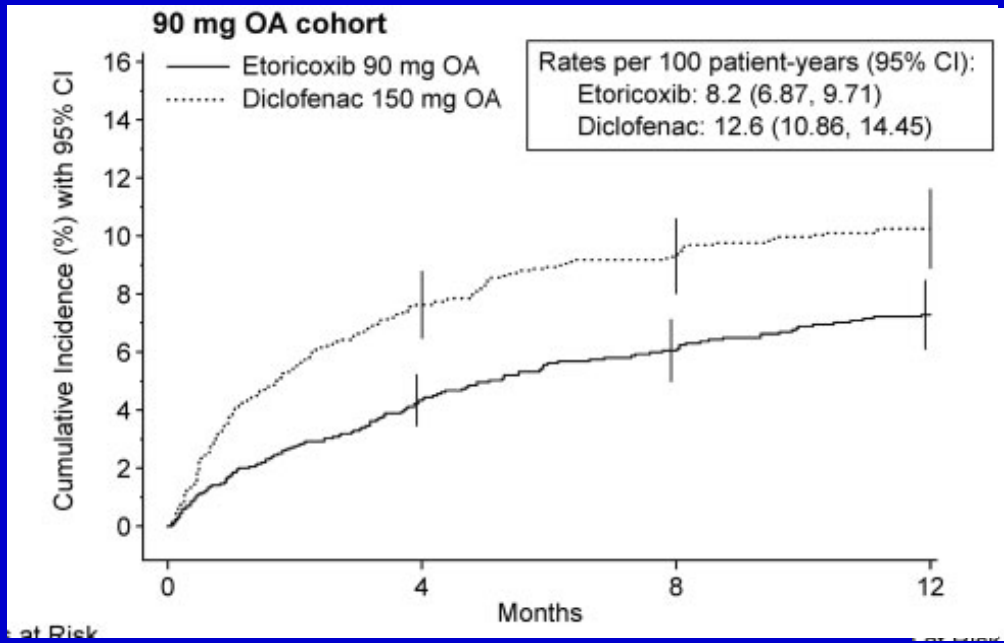


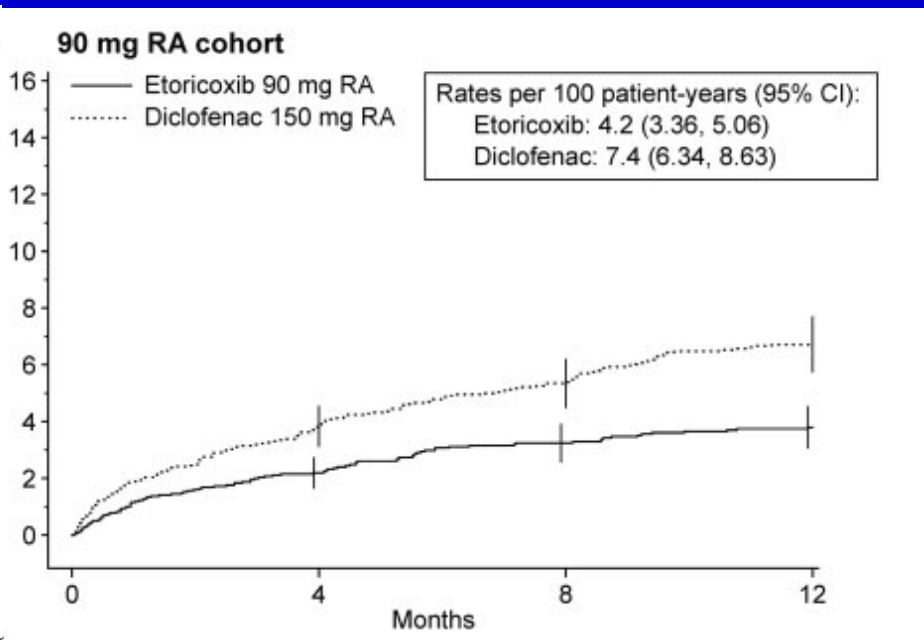


Cannon CP et al., Lancet 2006

Gastrointestinal Safety of Cox-2 versus NSAIDs (the MEDAL Study)

Cumulative discontinuations due to clinical GI AEs within 12 months.





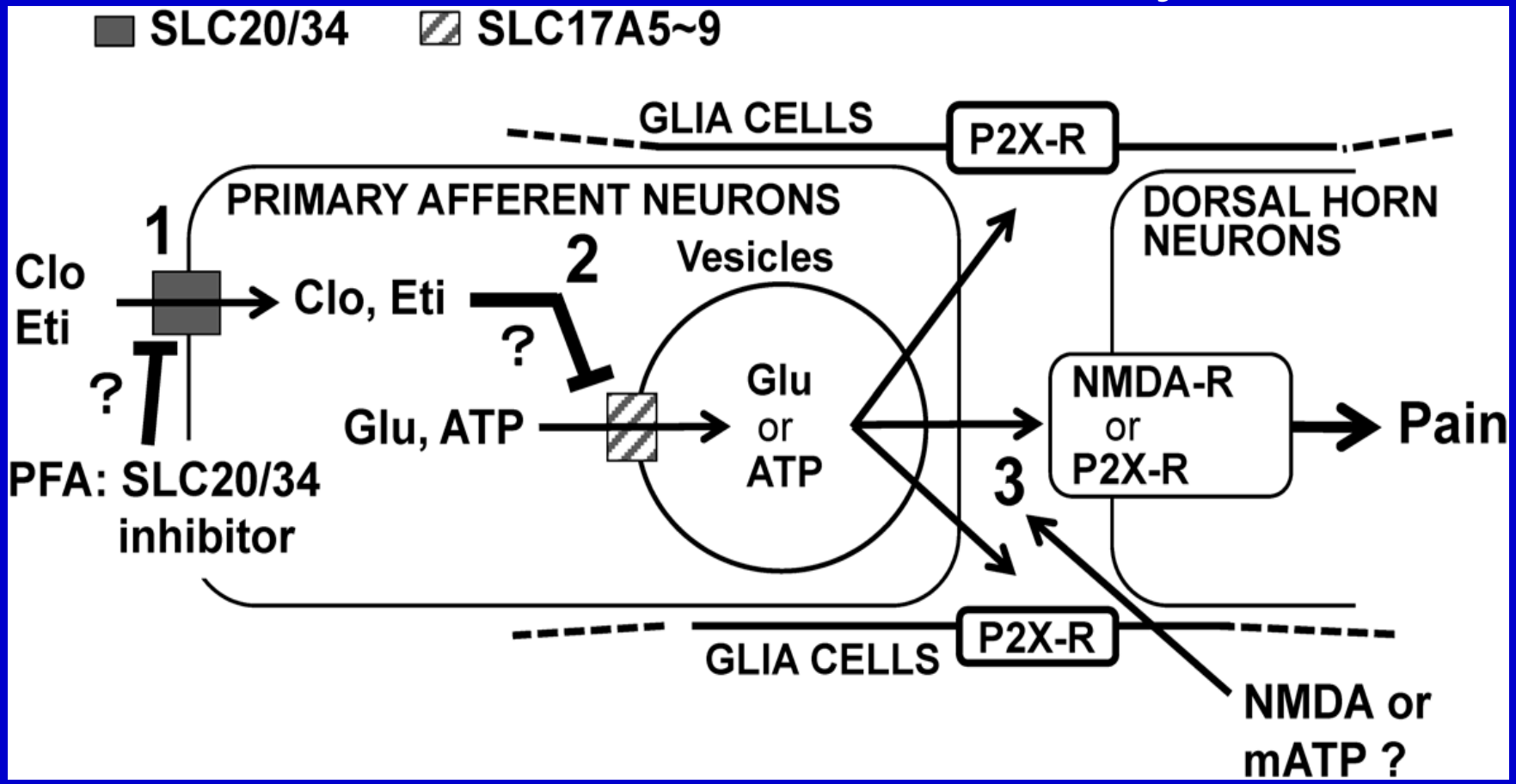
Combe B et al., Rheumatology 2009

Treatment
Of Musculoskeletal Pain
Bisphosphonates

Bisphosphonates & Pain: Potential Mechanisms

- ✓ High focal concentrations within bone & subcondral bone (high bone turnover or high blood flow)
- ✓ Inhibition protons secretion (e.g., osteoclasts in bone cancer)
- ✓ Inhibition of apatite crystals dissolution due to low local pH (e.g., CRPS-I)
- ✓ Significant anti-inflammatory effect within the bone marrow
- ✓ Inhibition of bone resorption mediated by osteoclasts
- ✓ Bone marrow cells cytotoxicity (impaired macrophage function and decreased PG and cytokine production)
- ✓ Inhibition of the glutamate- and/or ATP-Related pain transmission pathways

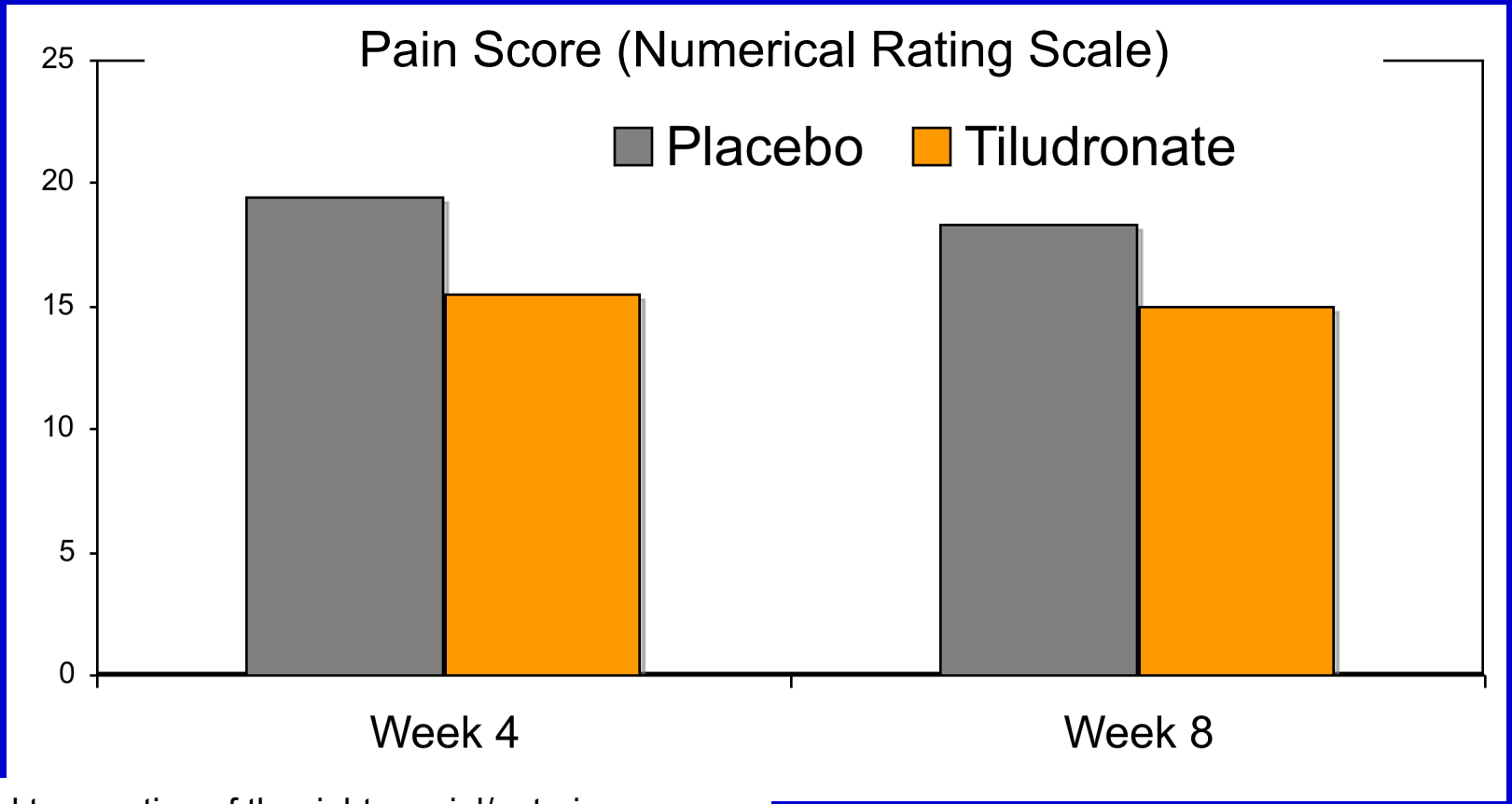
BPs Inhibit Glutamate- and/or ATP-Related Pain Transmission Pathways



Etidronate (Eti) and clodronate (Clo) are taken up into neurons via SLC20/34, they inhibit the transport of Glu and/or ATP, resulting in their decrease, and thus exhibit analgesic effects.

Shima K et al., Biol Pham Bull 2016

Tiludronate Improves OA Pain in the Canine Model

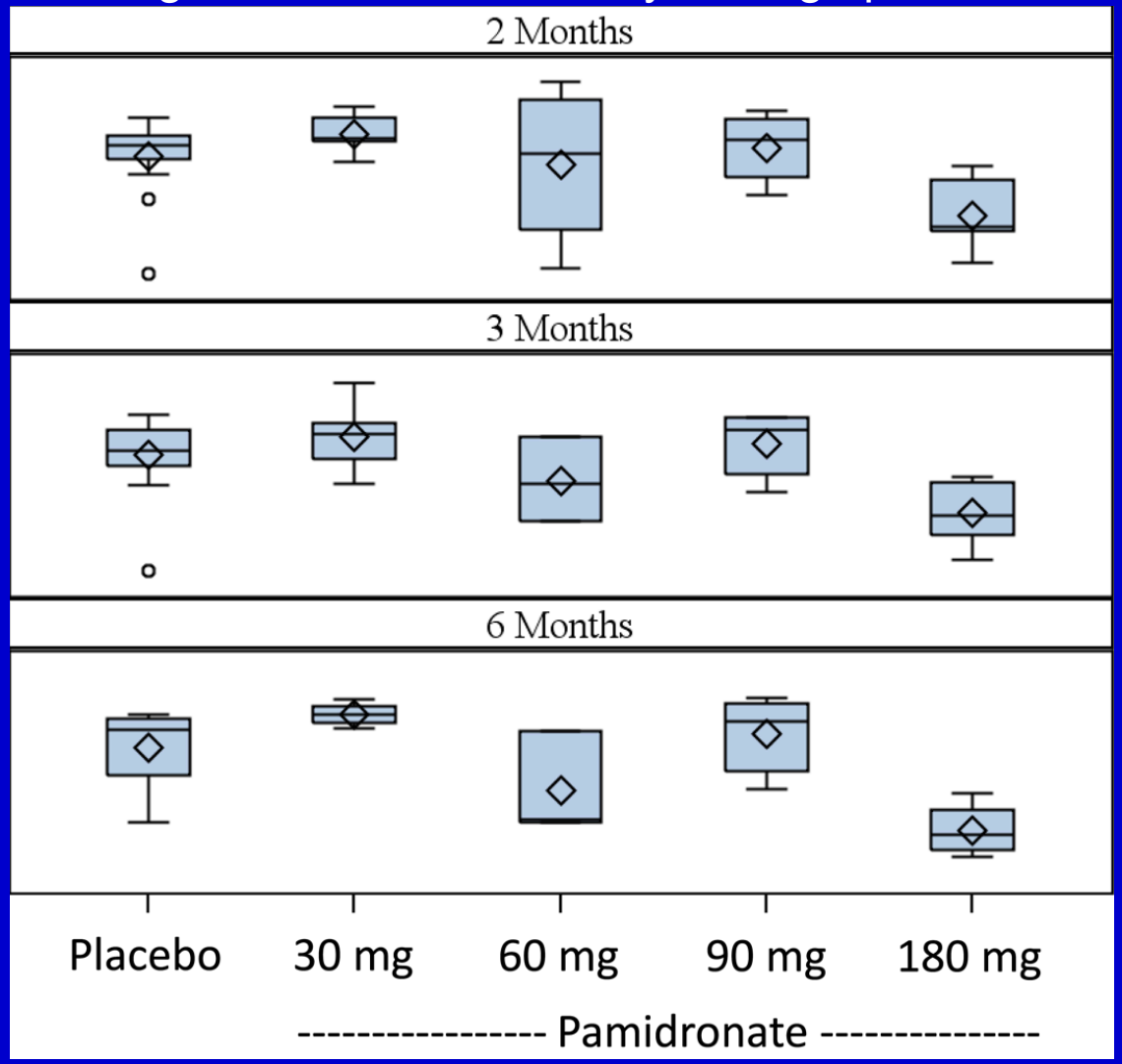


Surgical transection of the right cranial/anterior cruciate ligament, with eight dogs serving as OA placebo controls and eight others receiving four TLN injections

Moreau M et al., Arthritis Research & Therapy 2011

Pamidronate Reduces Chronic Low Back Pain

Change from baseline in daily average pain score



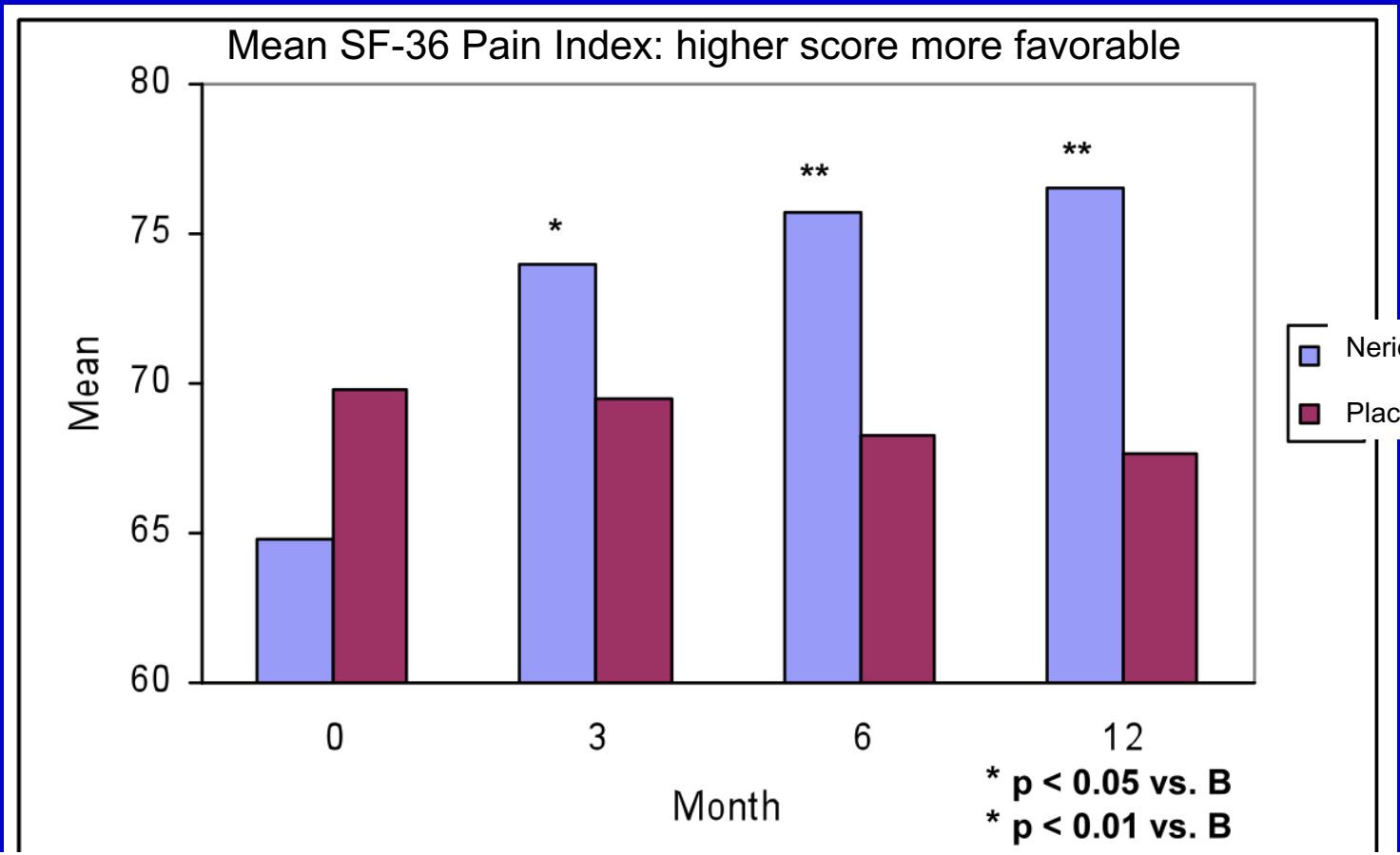
Least square mean changes in daily average pain score were:

Placebo −1.39 (SE=0.43)
PAM-30 −1.53 (0.71)
PAM-60 −1.26 (0.81)
PAM-90 −1.42 (0.65)
PAM-180 −4.13 (0.65)

(p=0.012 for pamidronate 180 mg versus placebo).

Pappagallo M et al., Pain 2014

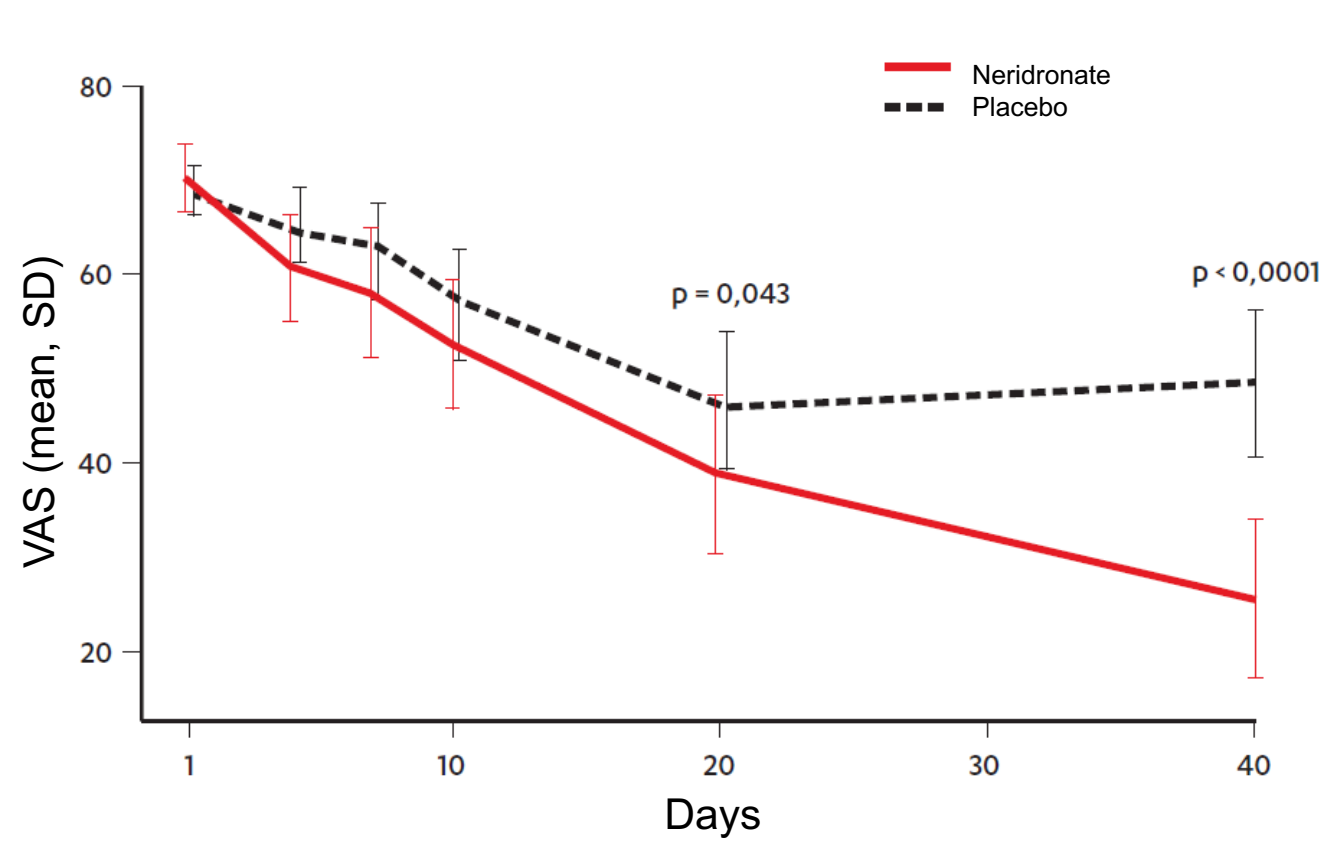
Neridronate Reduces Body/Back Pain in Thalassemic Patients



A concomitant significant reduction (50% group A, 30% group B) in the use of analgesic drugs was noted starting from the third month.

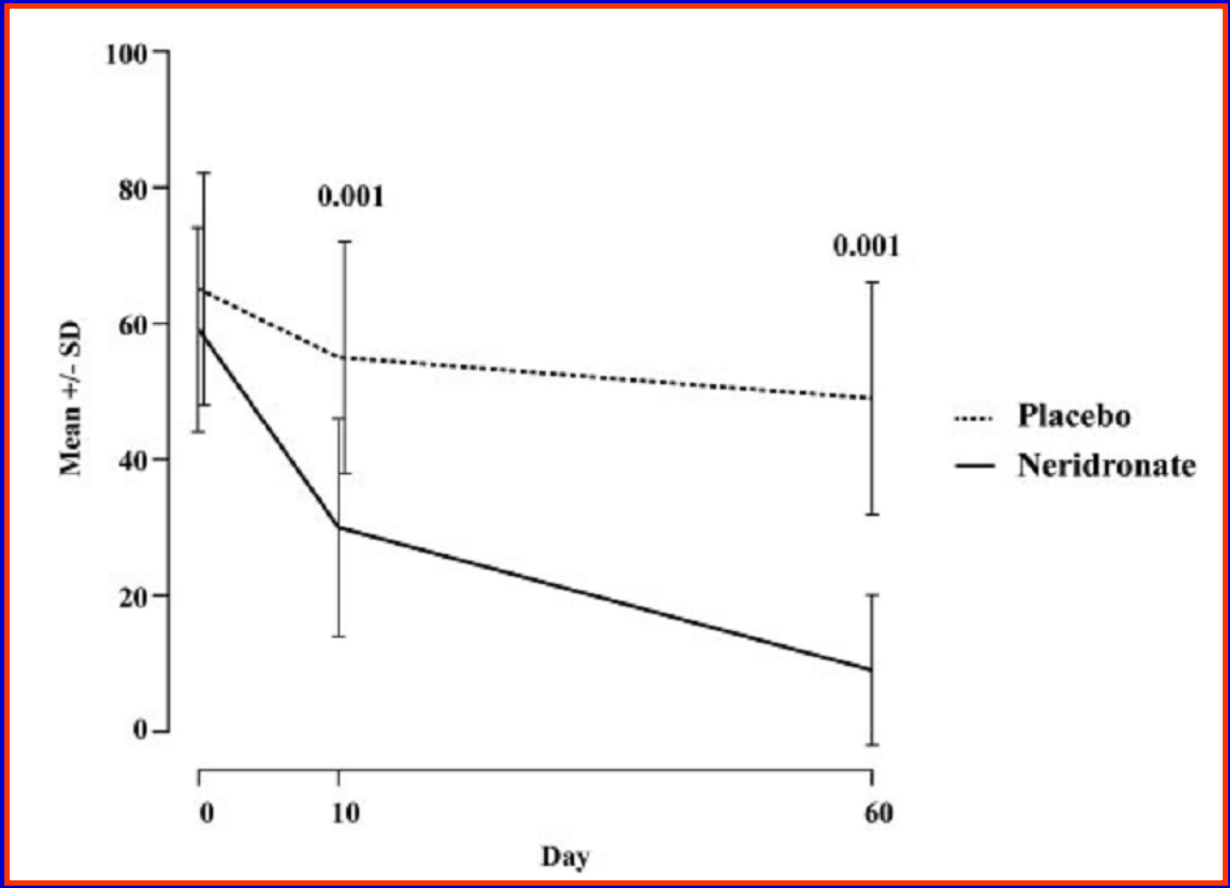
Forni GL et al., Br J Haematology 2012
Giusti A et al., Ann N Y Acad Sci 2016

Neridronate Reduces Pain in CRPS Type I



Varenna M et al., Rheumatology 2013

Neridronate Reduces Pain in Knee Osteoarthritis (with Bone Marrow Lesion)



Pain trend at baseline and after neridronate treatment or placebo

Varenna M et al., Rheumatology 2015

Conclusion

Musculoskeletal pain is a frequent disorder, particularly in older adults and in subjects presenting with complex and chronic diseases

The physiopathology of musculoskeletal pain is complex and heterogeneous, involving the peripheral and central nervous system and local factors

The management and treatment should be based and driven by the physiopathology, considering the use of different pharmacological agents

The bisphosphonates demonstrated to be effective in the treatment of pain in a variety of conditions