LOW-BACK PAIN AND ANTIDEPRESSANTS

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Conflicts of Interest

- Astellas
- Convergence
- Epitech
- Lilly
- Pfizer

Learning objectives

- Understanding the concept of mixed pain
- Low-back pain is almost always a mixed (nociceptive and neuropathic) pain
- The mechanism of action of the antidepressants is bound to be efficacious both in nociceptive and neuropathic pain
- Which are the best drugs according to an EBM literature survey

FIVE TYPES OF CHRONIC PAIN

- Nociceptive
- Neuropathic
- Psychogenic
- Idiopathic
- Mixed

FIVE TYPES OF CHRONIC PAIN

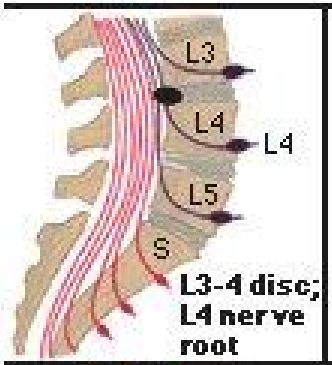
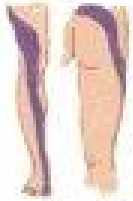
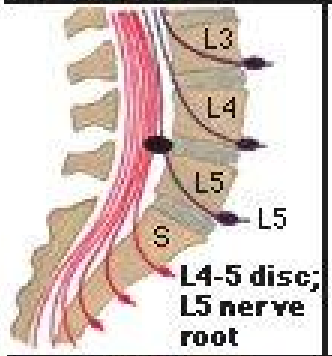
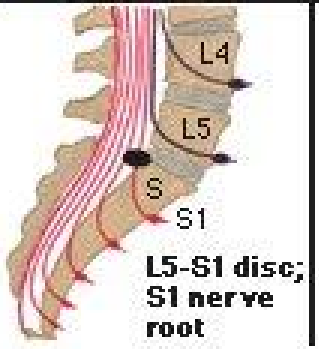
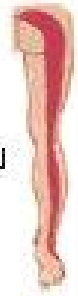
A PubMed search including papers published from inception date to 2011 showed how many articles used these terms:

- neuropathic pain: 7759
- nociceptive pain (378) or inflammatory pain (1868): 2246
- psychogenic pain (171) or somatoform pain (136) or pain behaviour (244): 551
- idiopathic pain: 74
- mixed pain: 46

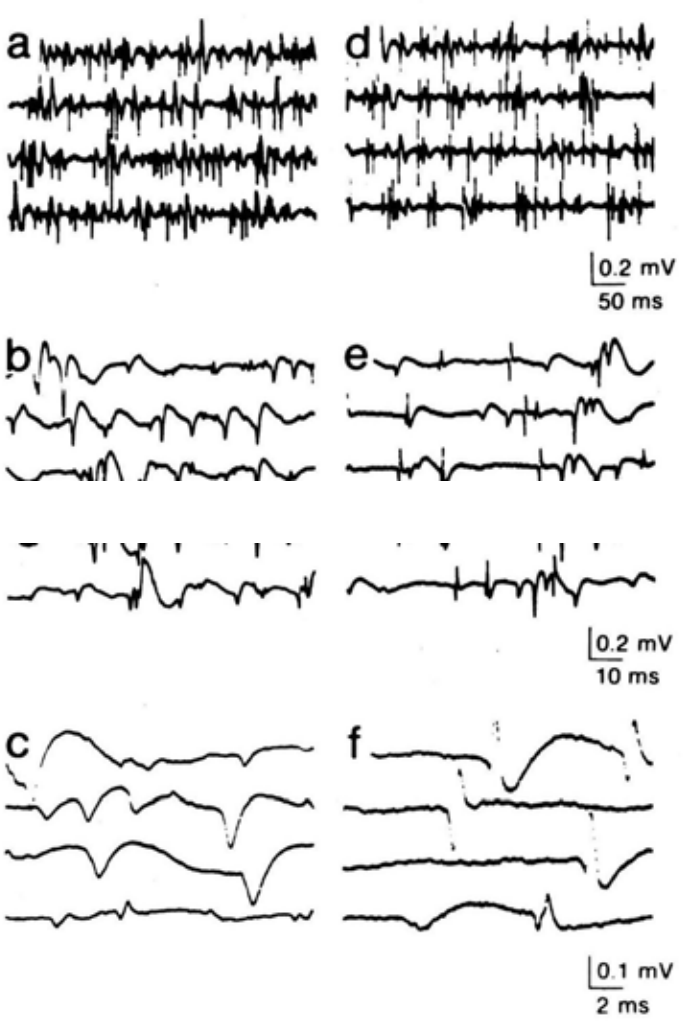
Clinical syndromes at lumbar level

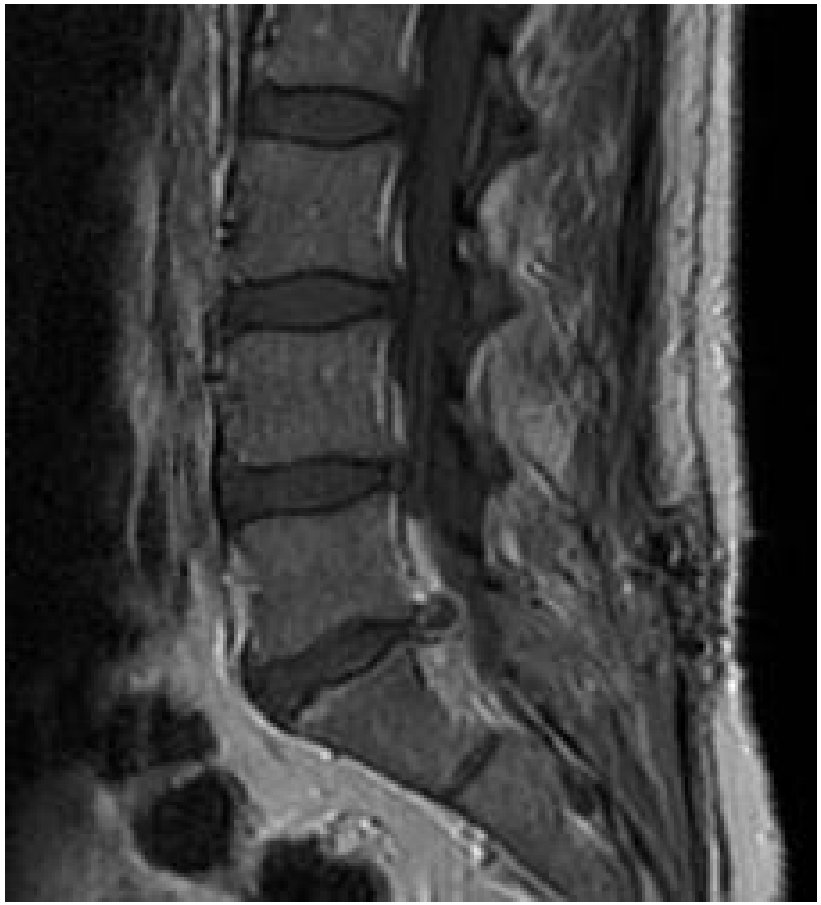
Lumbago	*muscle-skeletal pain*
Sciatica	*mixed pain due to radicular inflammation or compression*
Radiculopathy	*deafferentation neuropathic pain*
Failed Back Surgery Syndrome	*mixed pain with neuropathic pains of various type*

Clinical Manifestations of Lumbar Disc Herniation

Level of herniation	Pain	Numbness	Weakness	Atrophy	Reflexes
 **L3-4 disc; L4 nerve root**	 Lower back, hip, posterolateral thigh, anterior leg	 Anteromedial thigh and knee	 Quadriceps	 Quadriceps	 Knee jerk diminished
 **L4-5 disc; L5 nerve root**	 Above sacroiliac joint, hip, lateral thigh, and leg	 Lateral leg, first three toes	 Dorsiflexion of great toe and foot; difficulty walking on heels; foot drop may occur	Minor or nonspecific	Changes uncommon in knee and ankle jerks; posterior tibial reflex diminished or absent
 **L5-S1 disc; S1 nerve root**	 Over sacroiliac joint, hip, posterolateral thigh, and leg to heel	 Back of calf, lateral heel, foot and toe	Plantar flexion of foot and great toe may be affected; difficulty walking on toes	 Gastrocnemius and soleus	 Ankle jerk diminished or absent

Diagnostic investigations





The difference between coexisting pains and mixed pain

COEXISTING: caused by different diseases, supported by different mechanisms, and consequently treated independently.

MIXED: the same disease provokes different types of pain, which are difficult to separate and quantify, and thus entail difficulties in deciding the treatment strategy.

Clinical examples

A patient with syringomyelia involving the C5 dermatome who also has a periarthritis shoulder: two independent conditions that just happen to share a similar territory exist and must be independently managed.

A patient with trigeminal neuralgia affecting the mandibular division who has a coexisting temporomandibular disorder. This patient may report the typical electric shock-like attacks of trigeminal neuralgia and a dull, deep, and ongoing pain in the same territory and must therefore be distinguished from a patient with atypical trigeminal neuralgia, a neuropathic pain that entails both paroxysmal and background pain.

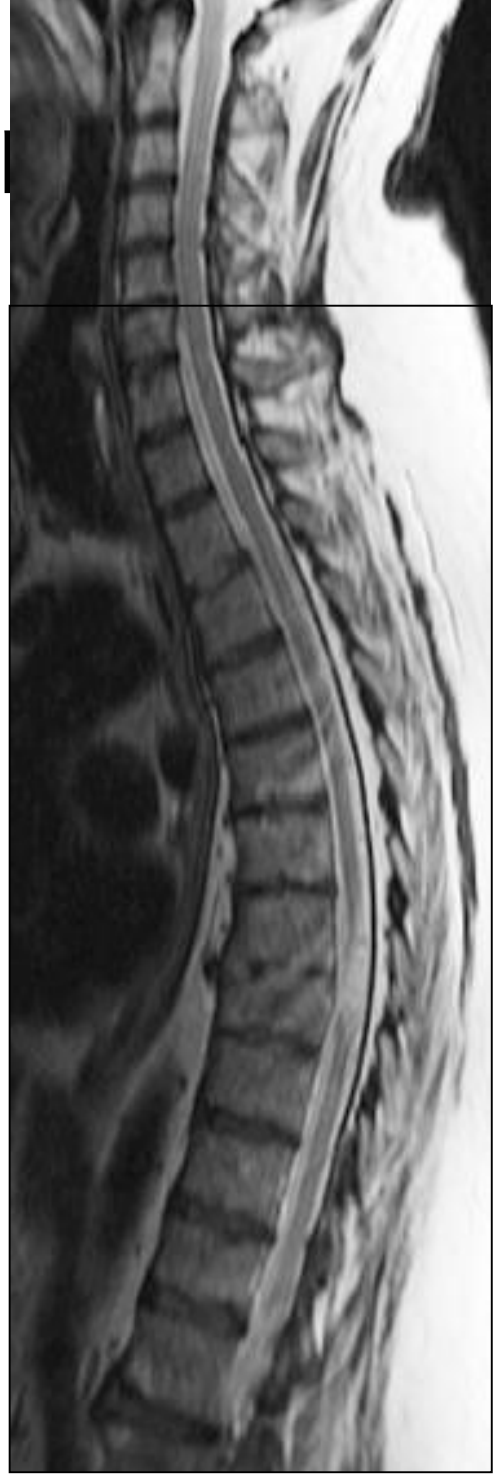
Neither patient has mixed pain.

Mixed Pains – different concep
“mixed”:

Mixed mechanism
Nerve trunk pain
Nerve inflammation

Neuropathic pain in
non-neurological diseases:
Cervicobrachialgia
Low-back pain
FBSS
Tumours

Nociceptive or mixed pains in
neurological diseases:
Muscle pain due to muscle hyperactivity
Joint pain induced by postural anomalies
after motor deficits

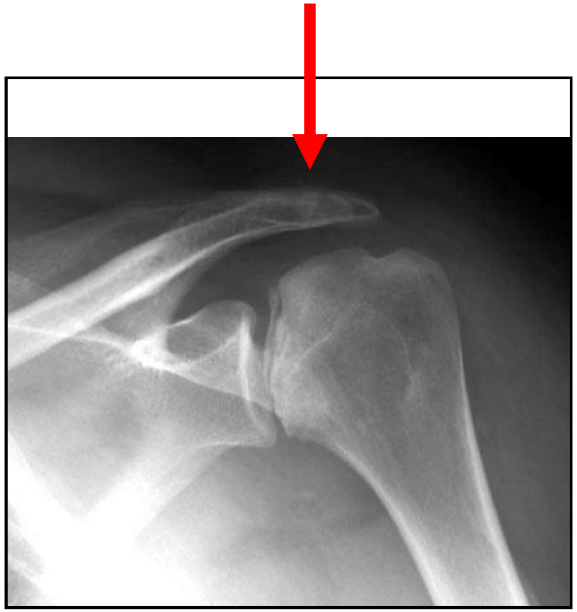


Nociceptive and mixed pains in neurological diseases:

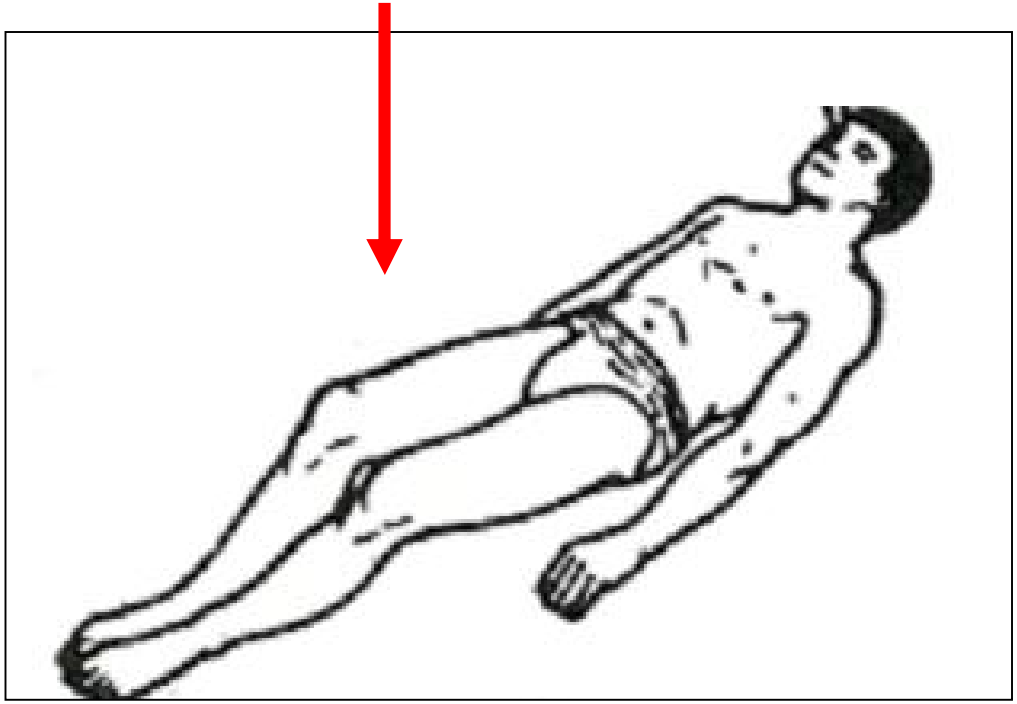
Muscle pain due to muscle hyperactivity

Joint and muscle pain induced by postural anomalies after motor deficits

Shoulder dystrophy in hemiplegia



Muscle spasms in multiple sclerosis



Low-back pain

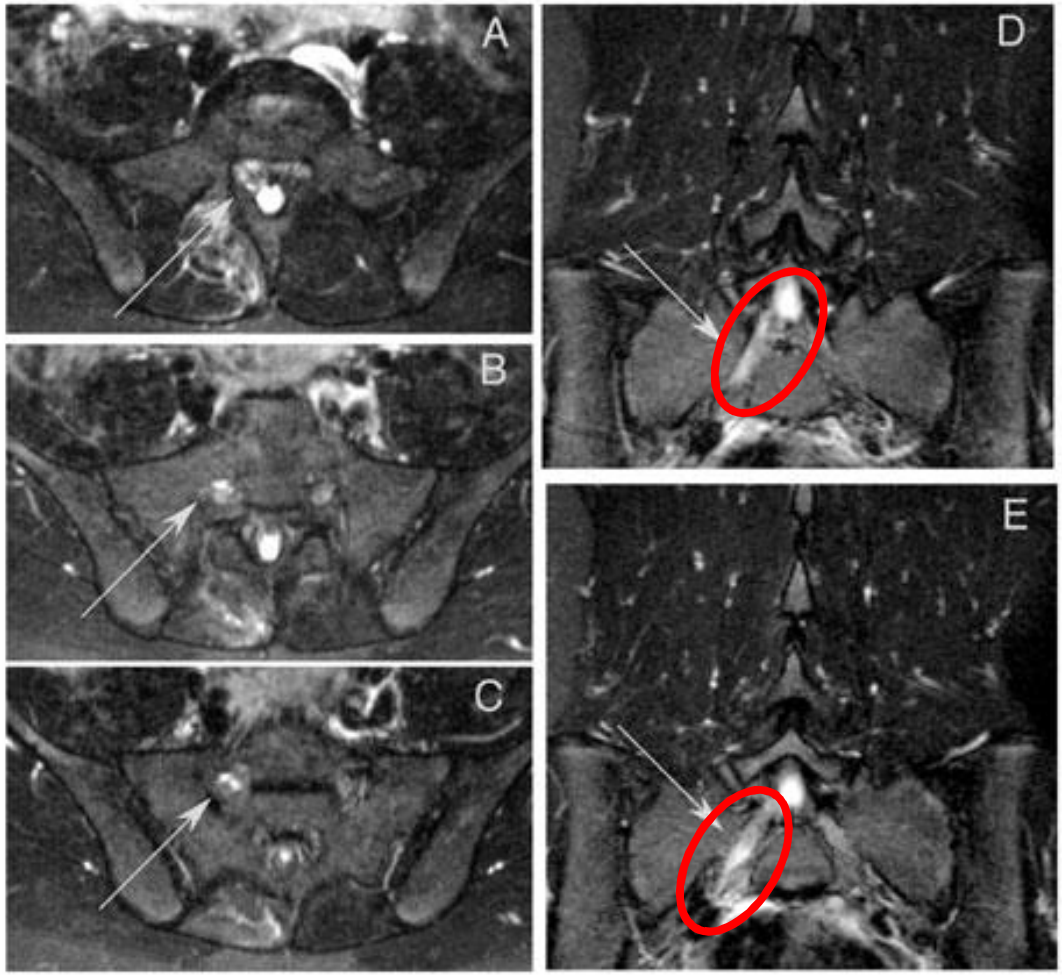
A frequent condition that fits the definition of mixed pain is low-back pain with sciatica, including both nociceptive components arising from muscles, ligaments, and joints, and neuropathic component arising from the spinal root. When the involved spinal roots innervate proximal territories the neuropathic and nociceptive components may be difficult to separate.

Besides spinal root compression, inflammatory mediators originating from the degenerative disc may induce radicular pain without any mechanical compression or nociceptive sprouts within the degenerated disc may give raise to local neuropathic pain

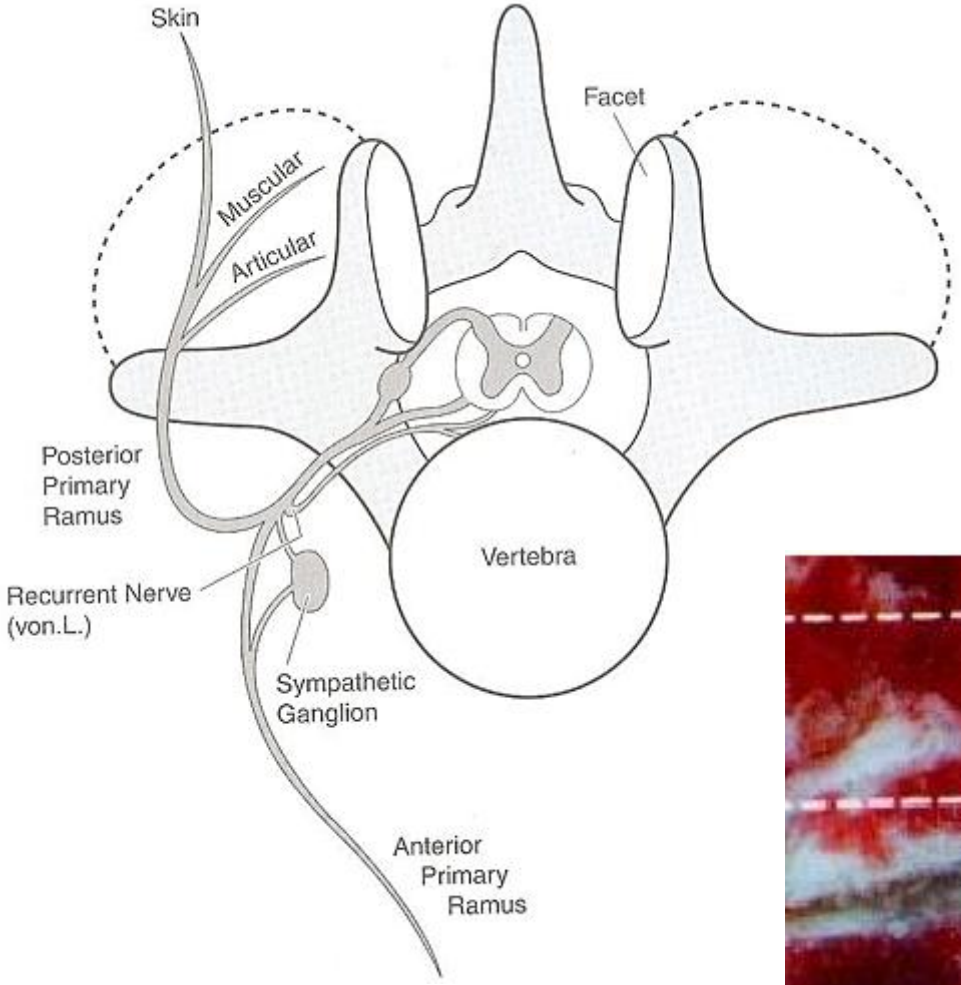
Freynhagen and Baron. The evaluation of neuropathic components in low back pain. Curr Pain Headache Rep 2009

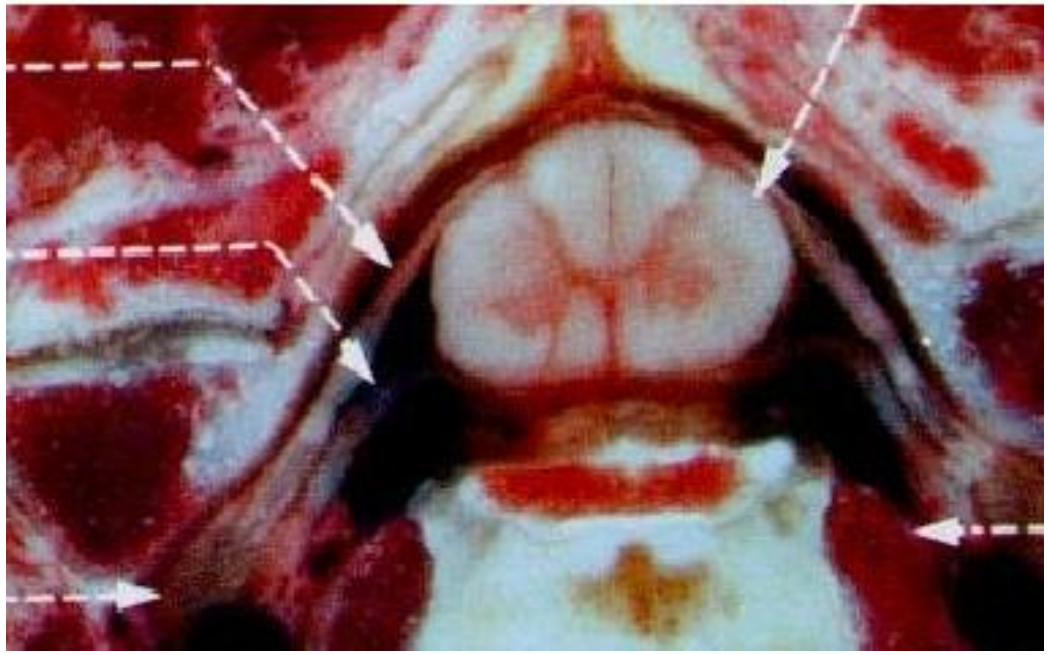
Back pain and Radiculitis

Two fascicles in the right S1 root are hyperintense as they descend from the root sleeve (A) and traverse the sacrum (B,C, D & E arrows). The contralateral S1 root is normal in appearance. The patient experienced focal pain in the calf. The symptoms resolved with dexamethasone.

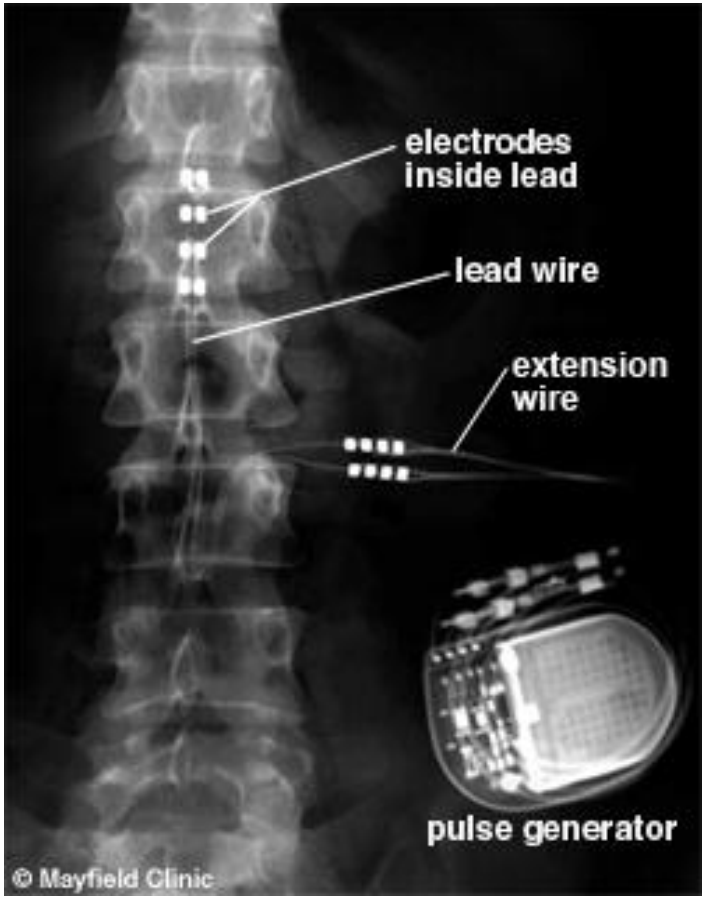


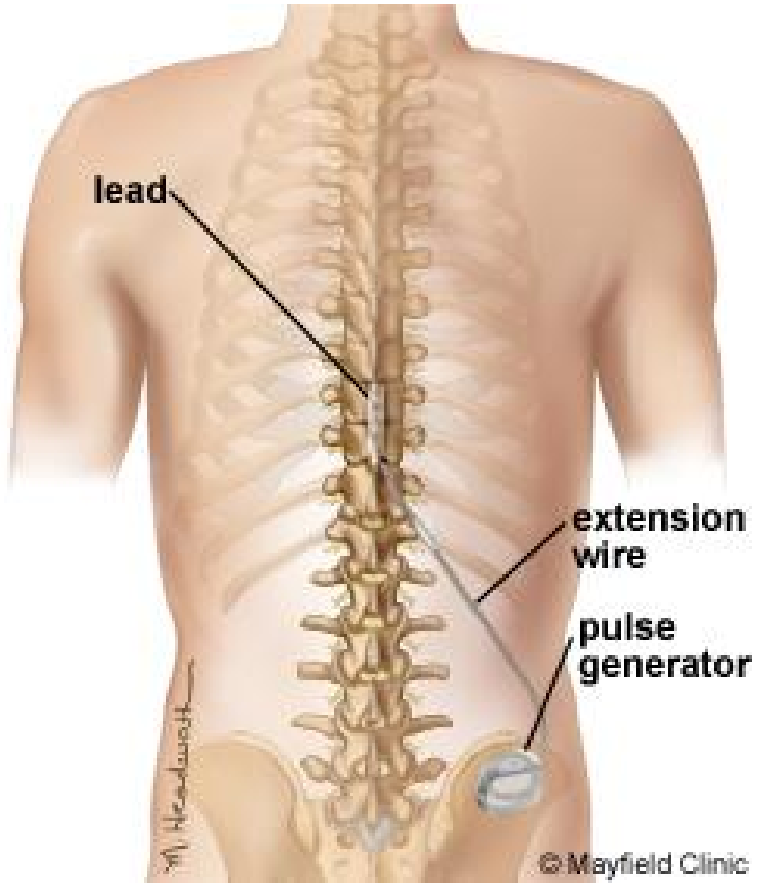
Luschka’s nerves





Spinal Cord Stimulation (EFNS Class A for FBSS)





Cruccu et al. EFNS Guidelines on Neurostimulation Therapy.

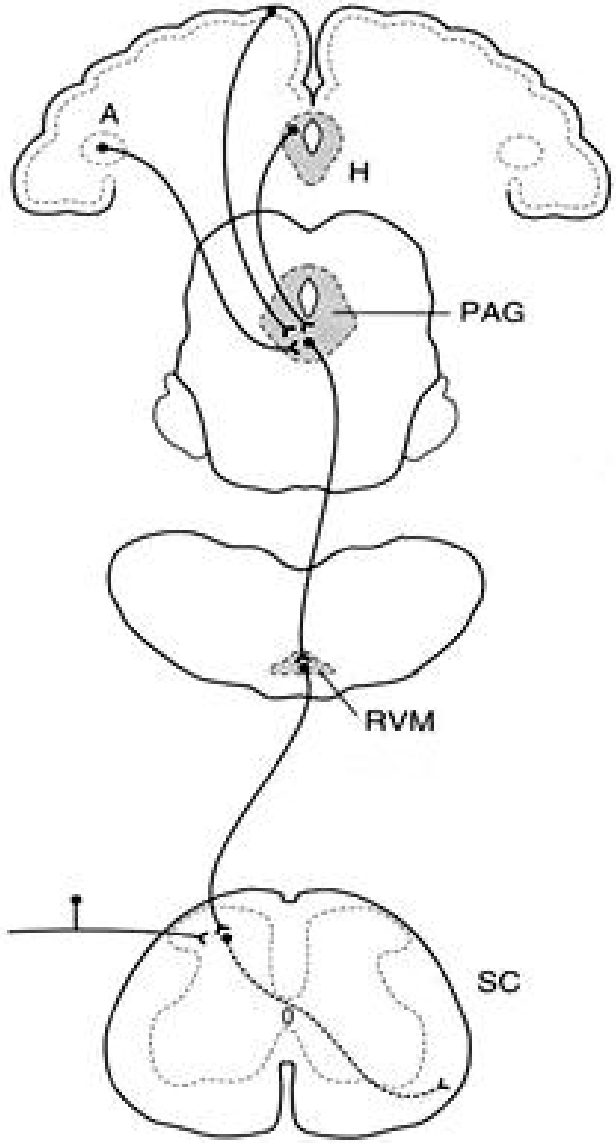
Eur J Neurol 2007

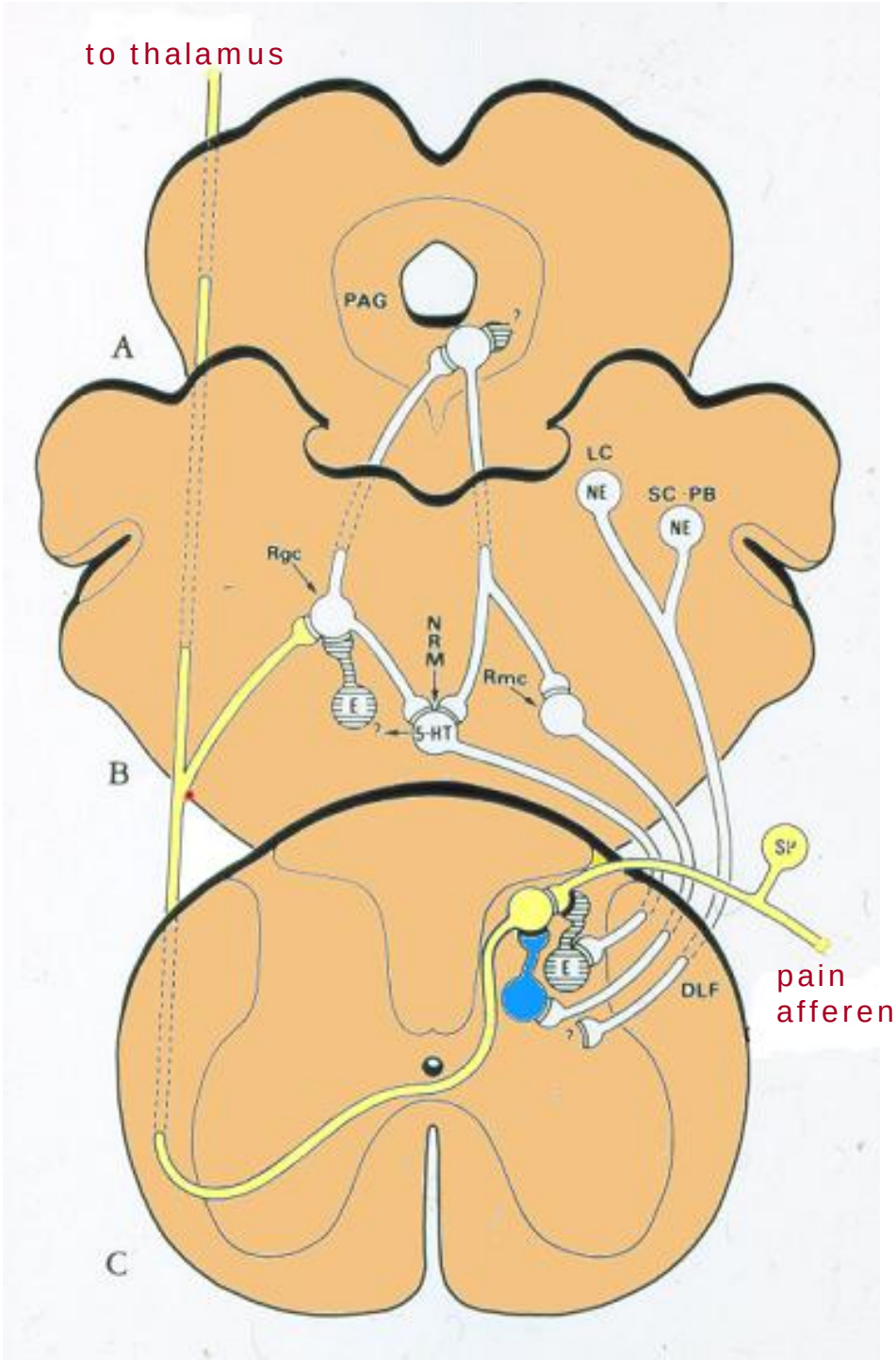
Table 2. Modern Screening Tools

Questionnaires	ID Pain	NPQ	PainDETECT	LANSS	DN4	StEP
Symptoms reported						
Ongoing pain						–
Pricking, tingling pins, needles (any dysesthesia)	+	+	+	+	+	+
Electric shocks or shooting	+	+	+	+	+	
Hot or burning	+	+	+	+	+	–
Numbness	+	+	+		+	
Pain evoked by light touching	+	+	+	+		
Painful cold or freezing pain		+			+	–
Pain evoked by mild pressure			+			
Pain evoked by heat or cold			+			
Pain evoked by changes in weather		+				
Pain limited to joints	–					
Itching					+	
Temporal patterns or temporal summation			+			–
Radiation of pain			+			
Autonomic changes	+					
Physical examination						
Abnormal response to cold temperature (decrease or allodynia)						+
Hyperalgesia						+
Abnormal response to blunt pressure (decreased or evoked pain)						+
Decreased response to vibration						+
Brush allodynia				+	+	–
Raised soft touch threshold					+	–
Raised pinprick threshold				+	+	+
Straight-leg-raising test						+
Skin changes						

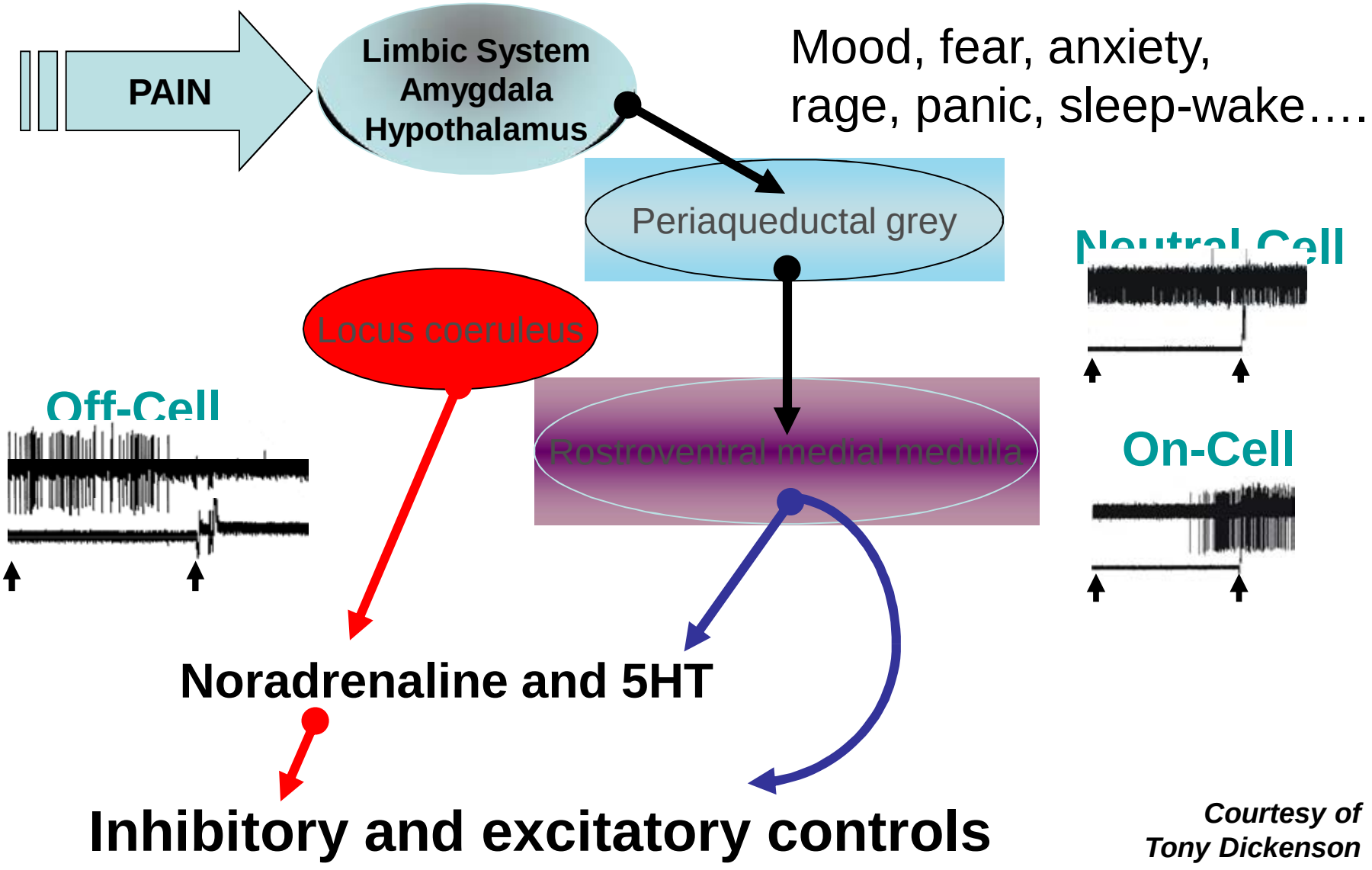
The (main) mechanism of action of the antidepressants provides the advantage that it is bound to be efficacious on any types of pain, independently from their pathophysiological mechanism

Modulating Descending System



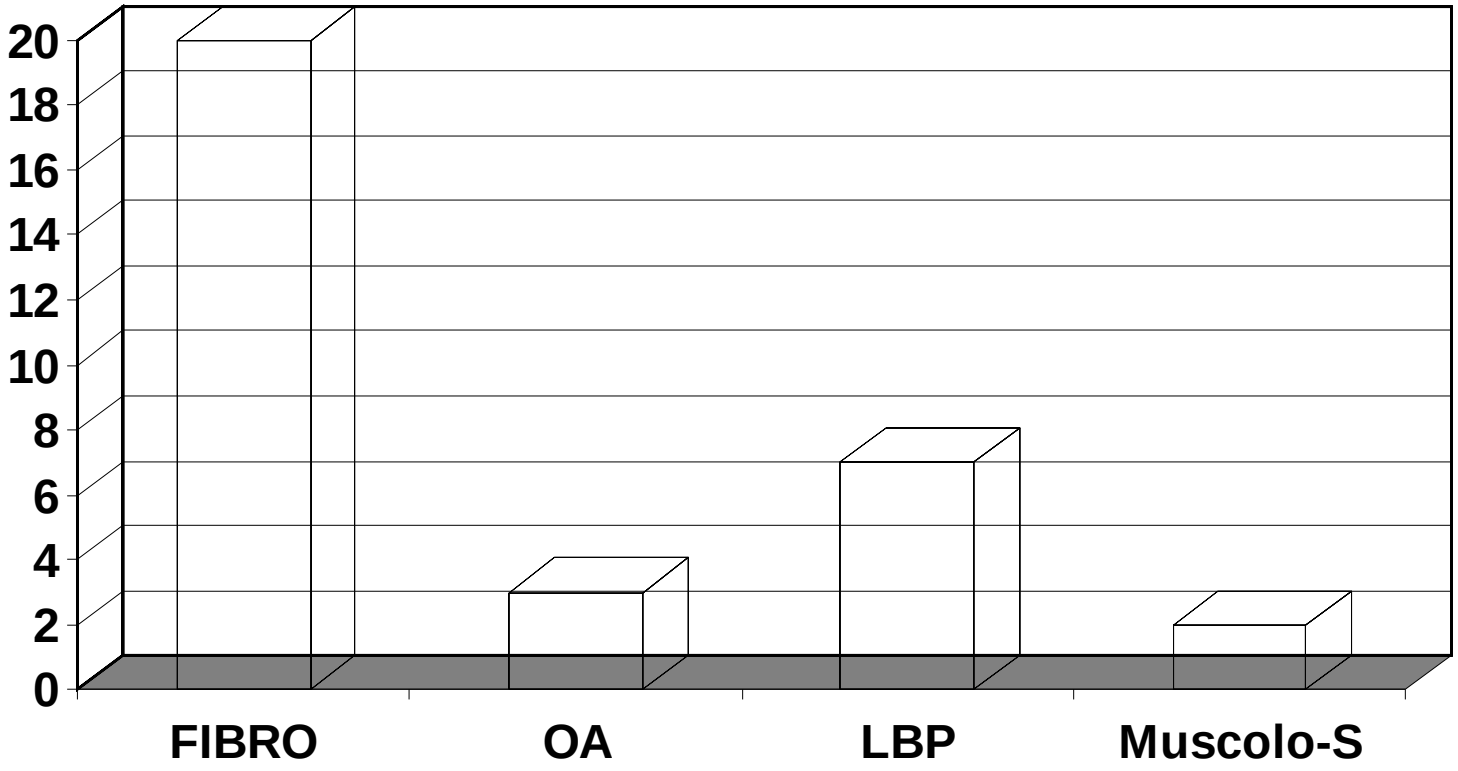


Noradrenaline and 5HT



Courtesy of
Tony Dickenson

Ramdomised controlled trials (RCT) with antidepressants in muscle-skeletal pains



Evidence of efficacy for tricyclic antidepressants

Khoromi et al. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007	RAD LBP	NEG
Katz et al. A randomized, placebo-controlled trial of bupropion sustained release in chronic low back pain. J Pain 2005	LBP	NEG
Schreiber et al. A randomized trial of fluoxetine versus amitriptyline in musculo-skeletal pain. Isr J Psychiatry Relat Sci. 2001	MIX	POS
Atkinson et al. A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. Pain 1998	LBP	INT
Pheasant et al. Amitriptyline and chronic low-back pain. A randomized double-blind crossover study. Spine 1983	LBP	POS

Evidence of efficacy for serotonin-noradrenaline reuptake inhibitors (SNRI)

Venlafaxine

Sullivan et al. A single-blind placebo run-in study of venlafaxine XR for activity-limiting osteoarthritis pain.

Pain Med. 2009

We performed a single-blind placebo run-in trial of 150-225 mg of venlafaxine in 18 subjects with activity-limiting osteoarthritis pain. Each subject received 2 weeks of placebo followed by 10 weeks of venlafaxine. The primary outcome was reduction in average pain intensity between 2 and 12 weeks. Average pain on the Brief Pain Inventory (BPI) was 4.7 at baseline, 4.4 after the 2-week placebo run-in, and 3.3 at 12 weeks (25% decrease, P = 0.03).

Duloxetine has been proved to be efficacious both on neuropathic and nociceptive pains

(*n*= ~2,500 patients)

Pain Condition	Label	Duration	Met primary endpoint (pain relief)	References
Dolore Neuropatico Diabetico (DPNP)	DPNP 1 DPNP 2 DPNP 3	12 settimane 12 settimane 12 settimane	ü ü ü	Goldstein ‘05 Wernicke ‘06 Raskin ‘05
Fibromialgia (FM)	FM 1 FM 2 FM 3 FM 4	12 settimane 12 settimane 6 mesi 6 mesi	ü ü ü -	Arnold ’04 Arnold ‘05 Russell ’08 Chappell ‘08
Osteoartrosi (OA)	OA 1 OA 2	13 settimane 13 settimane	ü ü	Chappell ’09 Chappell ’09
Low Back Pain (CLBP)	CLBP 1 CLBP 2 CLBP 3	13 settimane 13 settimane 12 settimane	ü - ü	Skljarevski ’08 Skljarevski ’09 Skljarevski ’10

Overview of Primary Outcome Results in CLBP

Statistical Significance of LS Mean Change in Average Pain Severity (DLX vs PBO) at endpoint	
	MMRM
CLBP-EN	**p=0.004**
CLBP-EO	p=0.110
CLBP-GC	**p=0.001**

[1]Chappell AS, et al. *Pain;*2009:146:253-60; [2]Chappell AS et al. *Pain Practice*;2011;11:33-41; [3]Skljarevski V, et al. *Spine;* 2010;35:E578-E585; [4]Skljarevski V, et al. *Eur J Neurol;*2009;16:1041-1048; [5]Skljarevski V, et al. *J Pain;*2010;11:1282-90.

Duloxetine in CLBP Studies

Primary Outcome: Average Pain Severity

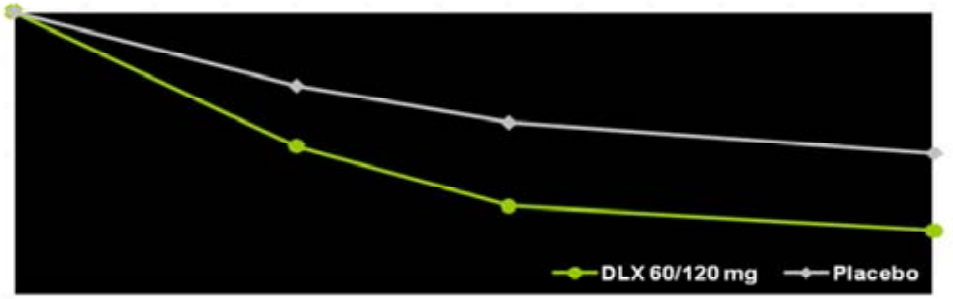
Duration: 13 weeks

[1]CLBP-EN

BPI Average Pain

DLX N=115

PLA N=121



[2]CLBP-EO

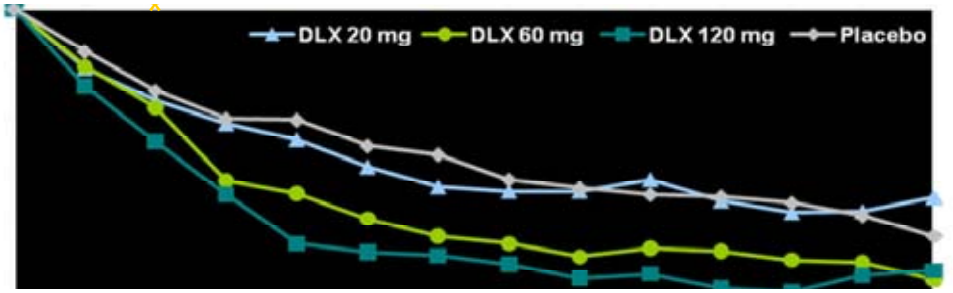
Weekly Mean 24-Hour Average Pain

DLX20 N=59

DLX60 N=116

DLX120 N=112

PLA N=117

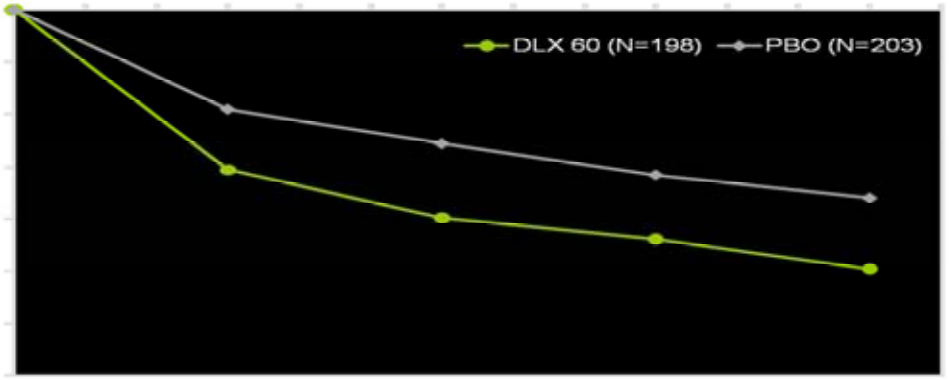


[3]CLBP-GC

BPI Average Pain

DLX60 N=198

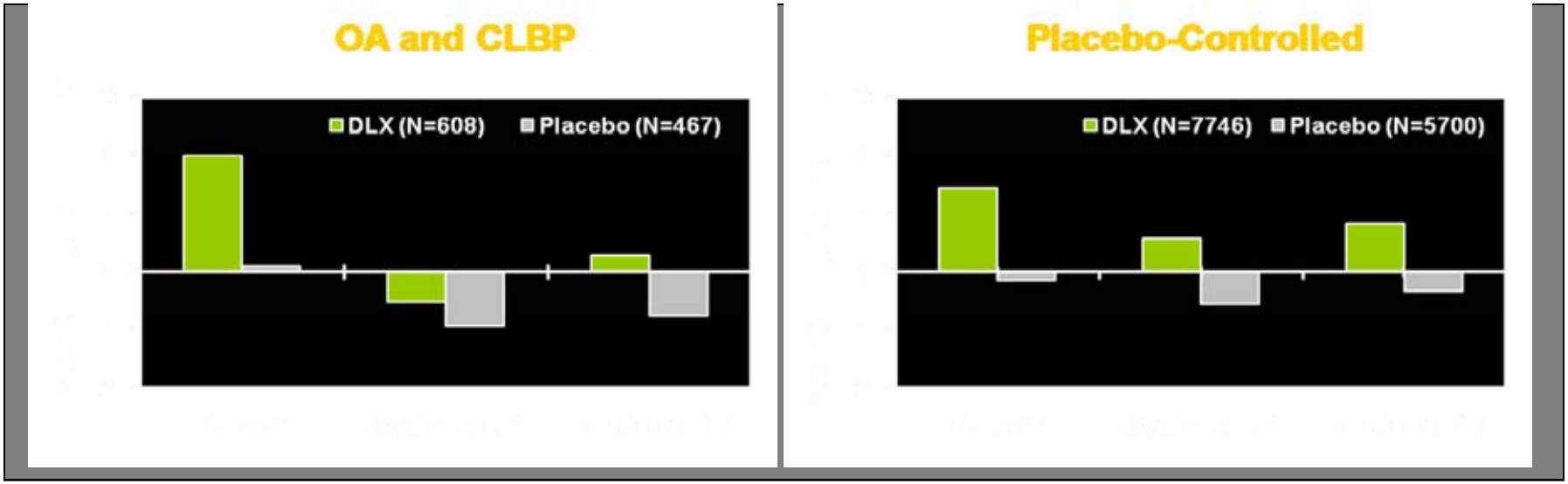
PLA N=203



*p?.05 vs Placebo

[1]Skljarevski V, et al. *Spine;* 2010;35:E578-E585; [2]Skljarevski V, et al. *Eur J Neurol;*2009;16:1041-1048.

Safety Data
Cardiovascular Effects (7746 patients)

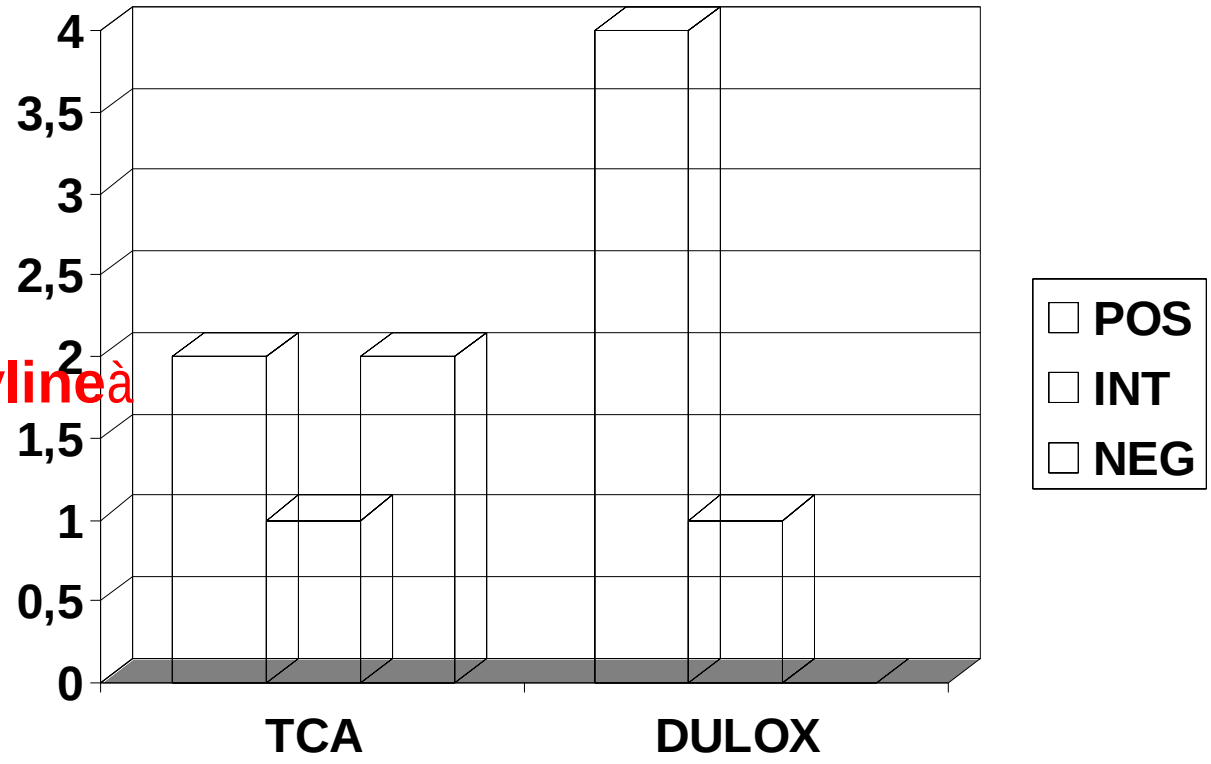


- Sustained hypertension:
  - No significant differences between DLX and placebo in either data set
- Potentially clinically significant cardiovascular changes:
  - No significant differences between DLX and placebo in either data set

Summary

- Bupropion, Citalopram insufficient or negative evidence
- Fluoxetine and Milnacipran only effective in Fibromyalgia
- Sertraline, Venlafaxine no evidence at all

- Amitriptylineà



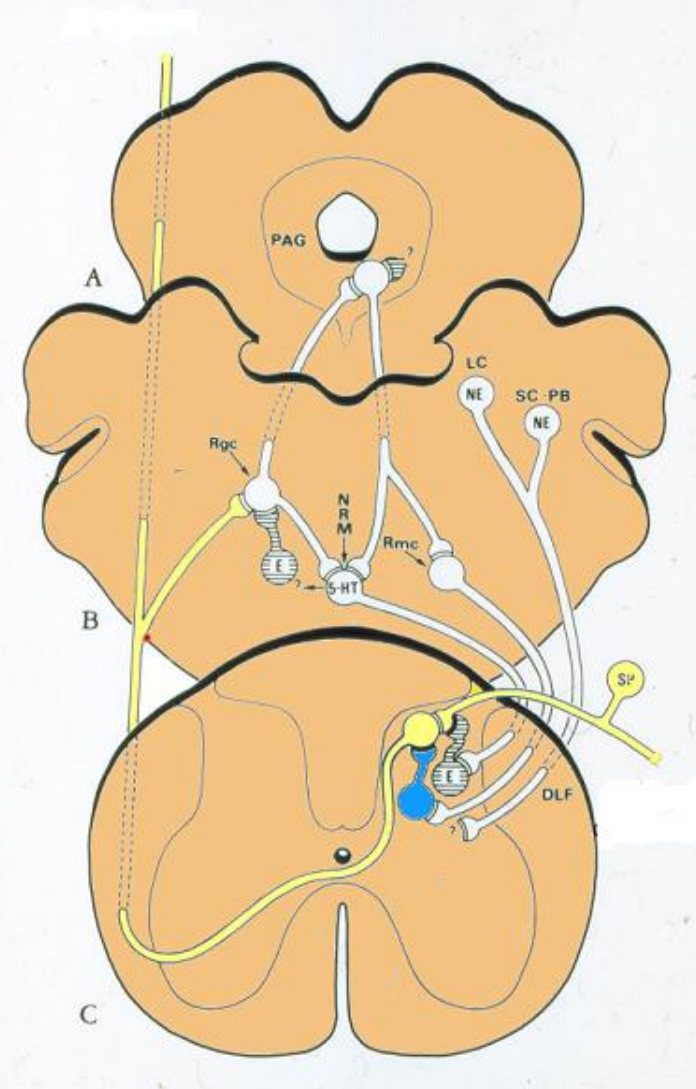
CONCLUSIONS

Low-back pain is often a mixed pain with nociceptive and neuropathic components that are difficult to disentangle and quantify

Antidepressant drugs, given their mechanism of action on the descending modulating system, are however able to be effective on the various pain components

Some antidepressant can be added in full safety to NSAIDs and may lead to a NSAIDs reduction

The choice of a specific antidepressant should be based on several considerations, which include the existence of EBM data of efficacy and the individual characteristics of the patient.



THANK YOU
FOR YOUR
ATTENTION

¿Tu cuerpo te da señales de dolor?

El dolor neuropático es un tipo de dolor que se manifiesta con sensaciones de **hormigueo, ardor profundo, descargas eléctricas o dolores punzantes** en el cuerpo. Describele a tu médico el tipo de dolor que sientes. Él puede recomendarte el tratamiento que Pfizer tiene para controlar este padecimiento.

www.dolorneuropatico.com
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