

Complications in Spine Surgery
Warwick June 2014



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Modern Trends in Pharmacological Treatment of Radiculitis

Mr M J H McCarthy
Consultant Spinal Surgeon

Fusion Portfolio Minimally Invasive Surgery Biomaterials Motion Preservation

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Wake Up Test

When you see it
don't spoil it, just hit like ;)



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Pain

- **A:** "a state of physical, emotional, or mental lack of well-being or physical, emotional, or mental uneasiness that ranges from mild discomfort or dull distress to acute often unbearable agony, may be generalized or localized, and is the consequence of being injured or hurt physically or mentally or of some derangement of or lack of equilibrium in the physical or mental functions (as through disease), and that usually produces a reaction of wanting to avoid, escape, or destroy the causative factor and its effects"
– Merriam-Webster 2014
- **B:** "a basic bodily sensation that is induced by a noxious stimulus, is received by naked nerve endings, is characterized by physical discomfort (as pricking, throbbing, or aching), and typically leads to evasive action"
– Merriam-Webster 2014

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Inflammation

- "a local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue"
– Merriam-Webster 2014

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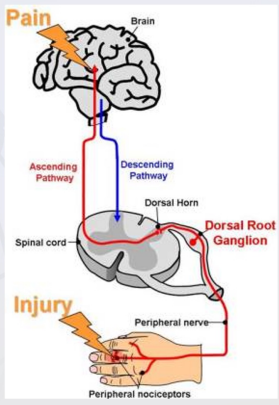
Radiculitis

- "inflammation of the root of a nerve"
– Merriam-Webster 2014
- Radicular pain, or radiculitis, is pain "radiated" along the dermatome (sensory distribution) of a nerve due to inflammation or other irritation of the nerve root (radiculopathy) at its connection to the spinal column
– Wikipedia 2014

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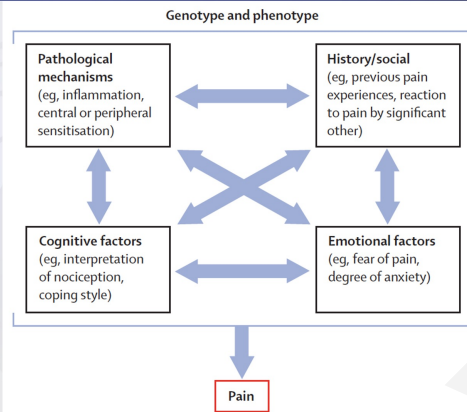
Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behaviour



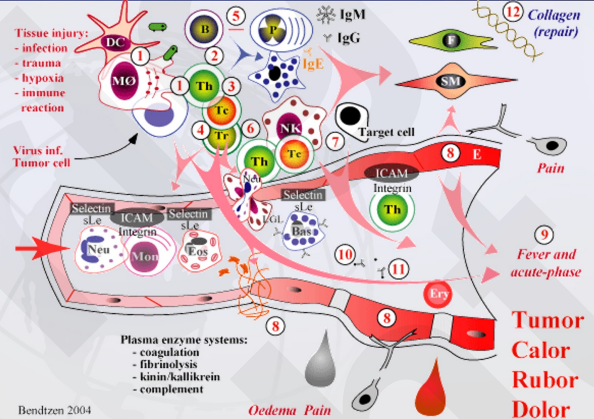
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Factors Contributing to Pain Severity



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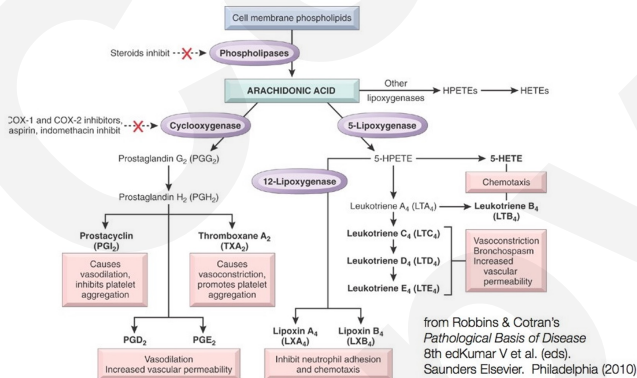
Inflammatory Pathways 1



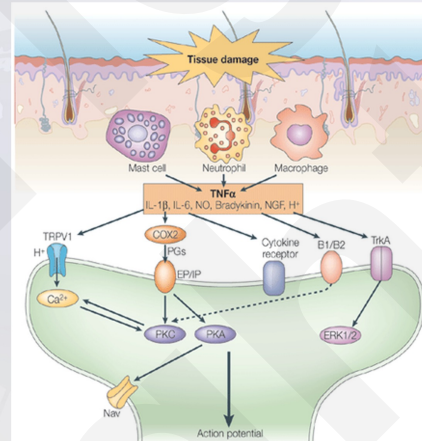
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Inflammatory Pathways 2

Arachidonic acid metabolites and inflammation



Simplified for Orthopods...



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...put in context

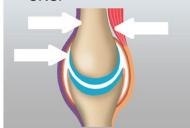
- Disc Herniates
 - Mechanical insult
 - Genetic predisposition
- Get inflammation +/- direct pressure on nerve
- Causes Pain

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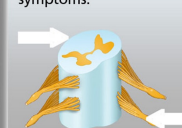
Inflammatory vs Neuropathic Pain

- Activity in neural pathways in response to potentially tissue damaging stimuli
- Initiated or caused by a primary lesion or dysfunction in the nervous system

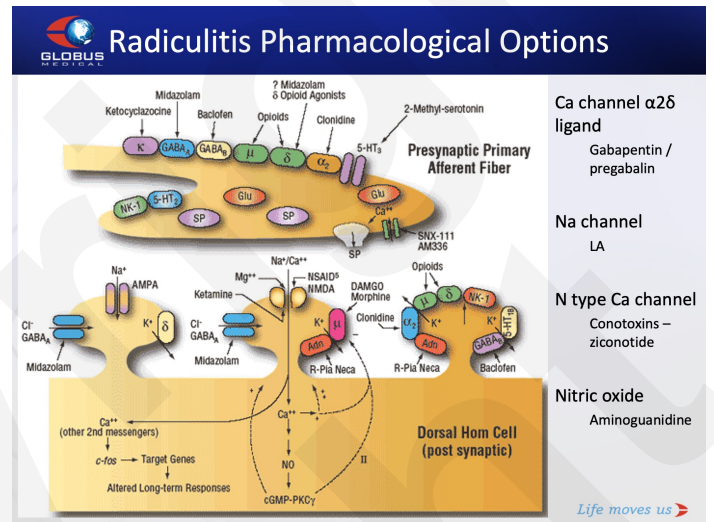
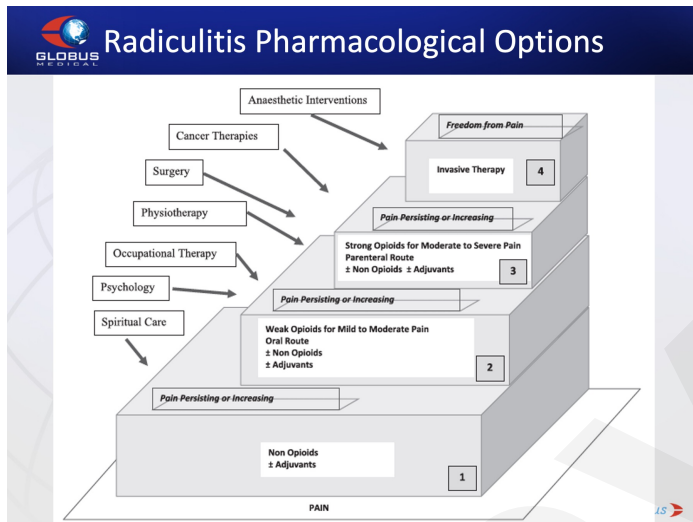
Nociceptive pain:
Nociceptors in tissues send pain signals to the CNS.



Neuropathic pain:
Damage to the nerve itself causes typical pain symptoms.



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Chronic Pain

- "pain that extends beyond the expected period of healing"
- > 3/12
- > 6/12
- > 12/12
- Neuroplasticity – maladaptive change – peripheral and central sensitization - somatotopic representation inappropriately reorganized

Medical Hypotheses (2007) 48, 74–80

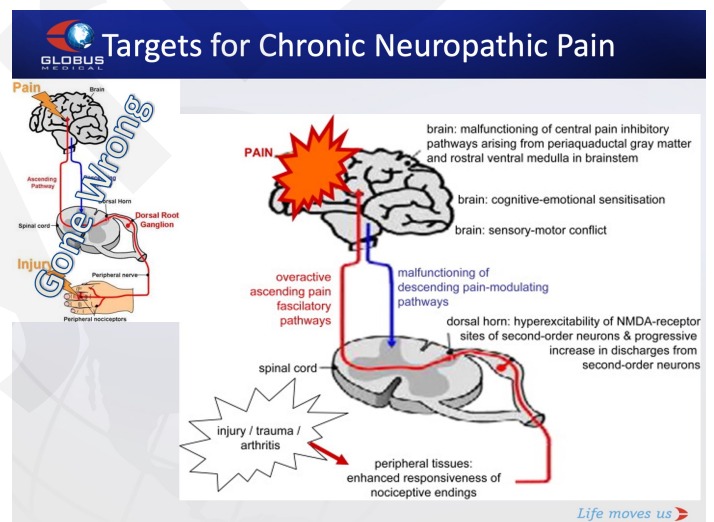
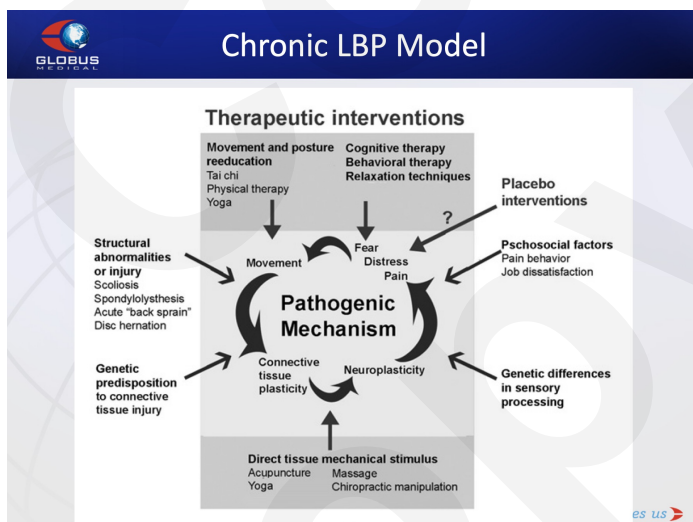
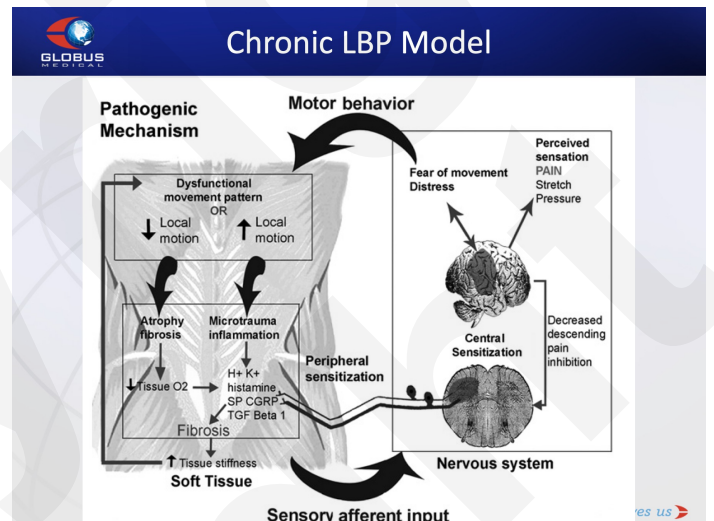
ELSEVIER

Pathophysiological model for chronic low back pain integrating connective tissue and nervous system mechanisms ☆

Helene M. Langevin ^{a,*}, Karen J. Sherman ^b

http://www.elsevier.com/locate/journal/mehy

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Targets for Chronic Neuropathic Pain

- Restore inhibitory neurotransmission
 - GABA
- Block peripheral sensitization
 - Na channels
- Block central sensitization
- Modulate Ca channels at $\alpha 2\delta$ subunit

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1 st Line Agents	Starting dosage	Titration	Maximum dosage	Duration of adequate trial
Secondary-amine TCAs Nortriptyline ^a or desipramine ^b (use tertiary amine TCA only if secondary amine TCA not available)	25 mg at bedtime	Increase by 25 mg/d every 3-7 d as tolerated	150 mg/d; if blood concentration of active medication and its metabolite is <100 mg/mL (mg/L), continue titration with caution	6-8 wk with at least 2 wk at maximum tolerated dosage
SSNRIs Duloxetine	30 mg once daily	Increase to 60 mg once daily after 1 wk	60 mg twice daily	4 wk
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg/d	4-6 wk
Calcium channel $\alpha_2\delta$ ligands Gabapentin ^b	100-300 mg at bedtime or 100-300 mg 3 times daily	Increase by 100-300 mg 3 times daily every 1-7 d as tolerated	3600 mg/d (1200 mg 3 times daily); reduce if impaired renal function	3-8 wk for titration plus 2 wk at maximum dose
Pregabalin ^b	50 mg 3 times daily or or 75 mg twice daily as tolerated	Increase to 300 mg/d after 3-7 d, then by 150 mg/d every 3-7 d as tolerated	600 mg/d (200 mg 3 times or 300 mg twice daily); reduce if impaired renal function	4 wk
Topical lidocaine 5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12-18 h	3 wk
2 nd Line = opioids Opioid agonists ^c Morphine, oxycodone, methadone, and levorphanol ^b	10-15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (eg, morphine at 120-180 mg/d; equianalgesic dosages should be used for other opioid analgesics)	4-6 wk
Tramadol ^d	50 mg once or twice daily	Increase by 50-100 mg/d in divided doses every 3-7 d as tolerated	400 mg/d (100 mg 4 times daily); in patients >75 y, 300 mg/d	4 wk

NeuPSIG 2010

- Neuropathic Pain Special Interest Group
- 3rd Line:
 - Other antidepressants
 - Bupropion, citalopram, paroxetine
 - Certain antiepileptics
 - Carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproate
 - Topical
 - Capsaicin, dextromethorphan, memantine, mexiletine
- Recent trials
 - Botulinum toxin
 - Lacosamide

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- NSAIDs, corticosteroids, antidepressants, anticonvulsants, muscle relaxants and opioids
- “Conclusions: As the existing evidence from clinical trials is of low quality, the efficacy and tolerability of drugs commonly prescribed for the management of sciatica in primary care is unclear.”

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2013

Gabapentin and Pregabalin in the Management of Postoperative Pain After Lumbar Spinal Surgery

A Systematic Review and Meta-analysis

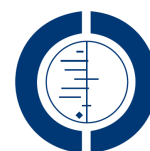
Lin Yu, MD,* Bo Ran, MD,† Min Li, MD,* and Zhicai Shi, MD†

- 7 studies included
- Both drugs significantly reduce post op pain during day 1 and reduce need for opiates

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Combination pharmacotherapy for the treatment of neuropathic pain in adults (Review)

Chaparro LE, Wiffen PJ, Moore RA, Gilron I



THE COCHRANE
COLLABORATION®

2012

- 45%+ pts with neuropathic pain on >2 drugs
- Poor evidence for most things
- Gabapentin + Opiate > Gabapentin alone

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Neuropathic Pain and Pharmacological Treatment

Joost L. M. Jongen, MD, PhD^{*†}; Guy Hans, MD, PhD[‡];
Honorio T. Benzon, MD, FIPP[§]; Frank Huygen, MD, PhD, FIPP[¶]; Craig T.
Hartrick, MD, FIPP^{**}

Symptom	Pathophysiological Mechanism	Most Suitable Medicine
Paroxysmal shooting or stabbing pain	Ectopic activity in nociceptive unmyelinated C fibers	Anticonvulsants Anti-arrhythmics
Spontaneous (continuous) burning pain	Sensitization of peripheral receptors, ectopic discharges in C fibers and disconnection of descending pain-inhibiting pathways	Tricyclic antidepressants Topical anesthetic drugs IV lidocaine or infiltration Tricyclic antidepressants
Dysesthesia	Ectopic discharges in thick myelinated (A- δ) nerve fibers	Anticonvulsants Drugs with inhibiting influence on sodium channels
Paresthesias	Spontaneous, ectopic discharges in different types of nerve fibers, going from A- δ fibers to the thin myelinated A- δ fibers, and in the unmyelinated C fibers	Anticonvulsants Anti-arrhythmics Tricyclic antidepressants Membrane-stabilizing drugs
Allodynia	Complex combination of different mechanisms, such as central reorganization (with implementation of ectopic impulses) of A- δ fibers, central sensitization of A- δ fibers, loss of descending inhibiting control	Anticonvulsants Tricyclic antidepressants Anticonvulsants Baclofen Opioids Clonidine
History and type of pain is important in treatment		Tricyclic antidepressants NMDA antagonists Local anesthetics

Study	Drug	Condition	Nature of Study	Efficacy
Gilron et al. ⁶²	Gabapentin + morphine	PHN, DPN	P, R, C	Positive
Gilron et al. ⁵⁶	Gabapentin + nortriptyline	PHN, DPN	P, R, C	Positive
Baron et al. ⁵⁷	Gabapentin + lidocaine plaster	PHN, DPN	P, R, C	Positive
Hanna et al. ⁶³	Gabapentin + oxycodone	DPN	P, R, C	Positive
Zin et al. ⁶⁴	Oxycodone + pregabalin	PHN, DPN	P, R, C	No difference
Khoromi et al. ⁵⁴	Morphine + nortriptyline	Lumbosacral radiculitis	P, R, C	No difference
Mercadante et al. ⁵⁵	Morphine + amitriptyline	Neuropathic cancer pain	P, R, C, Crossover	No difference

C, controlled; DPN, diabetic painful neuropathy; P, prospective; PHN, postherpetic neuralgia; R, randomized.

- Different combinations vary in efficacy

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Radiculitis Pharmacological Options



- Interlaminar
- Transforaminal (best)
- Caudal
- What to inject...

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Systematic Review

e Effectiveness of Therapeutic Lumbar Transforaminal Epidural Steroid Injections in Managing Lumbar Spinal Pain

Laxmaiah Manchikanti, MD¹, Ricardo M. Buenaventura, MD², Kavita N. Manchikanti, MD¹,
Xiulu Ruan, MD⁴, Sanjeeva Gupta, MD⁵, Howard S. Smith, MD⁶, Paul J. Christo, MD⁷, and
Stephen P. Ward, MD⁸

- 27 studies
- Evidence is:
 - good for radiculitis secondary to disc herniation with LA+steroid
 - fair for LA only
 - fair for spinal stenosis with LA+steroid

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RANDOMIZED TRIAL

antiTNF α

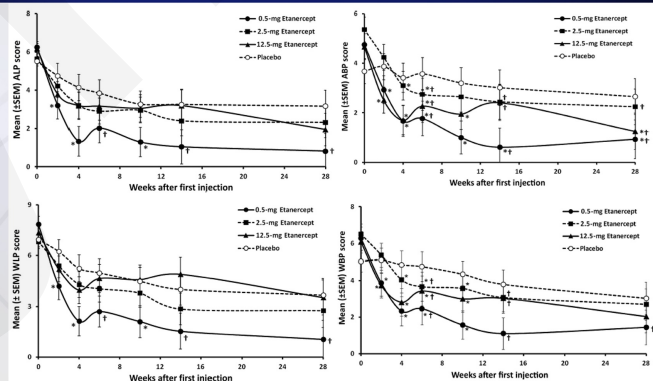
Randomized, Double-blind, Placebo-Controlled, Trial of Transforaminal Epidural Etanercept for the Treatment of Symptomatic Lumbar Disc Herniation

Brian J. C. Freeman, FRCS (Tr & Orth), FRACS (Ortho), DM,†† Guy L. Ludbrook, FANZCA, PhD,†† Stephen Hall, FRACP,† Michael Cousins, FANZCA, FFPANZCA,§ Bruce Mitchell, FACS, FACS, MPainMed,¶ Mark Jaros, PhD,|| Michael Wyand, DVM, PhD,** and James R. Gorman, MD, PhD**

- Phase 2a clinical trial
- 43/49 pts 18-70yrs radicular pain disc herniation >5/10
- Randomized 0.5mg, 2.5mg, 12.5mg etanercept vs placebo
- ITT – 10 / 12 / 13 / 8
- PP – 10 / 8 / 10 / 9
- Multicentre double blind
- 2 injections 2 weeks apart (?why)

Small numbers

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- Low dose etanercept reduced both leg and low back pain
 - Need phase 3 trials
- Life moves us 

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SPINE Volume 36, Number 5, pp E293-E300
©2011, Lippincott Williams & Wilkins

2011

a2 blocker

Spine
RANDOMIZED TRIAL

Transforaminal Epidural Clonidine Versus
Corticosteroid for Acute Lumbosacral
Radiculopathy due to Intervertebral
Disc Herniation

Abram H. Burgher, MD,* Bryan C. Hoelzer, MD,† Darelle R. Schroeder, MS,† Gregory A. Wilson, RRT,† and
Marc A. Hurlburt, MD†

- 26 pts disc herniation
- 11 clonidine vs 15 tramadol variable doses
- 2 injections 2-4/52 (why?)
- Both groups improved at 1/12
- Steroid better

New 4 year study coming from Exeter...

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Visual Analog Scale

Time of examination	Group I (VAS)	Group II (VAS)
Pre	~74	~74
Post	~33	~40
1 week	~34	~47
1 month	~32	~52
3 months	~36	~58
6 months	~38	~58
9 months	~38	~60
12 months	~42	~62



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- 100 pts enrolled
- 48 chymo 52 surgery
- 10 chymo to surgery within 8/52
- Good or excellent results:
 - 1 yr 94% vs 96%
 - 10-13yrs 72% vs 72% (31 vs 29 pts)
 - 24-27yrs 63% vs 67% (24 vs 21 pts)
- As effective as surgery in ITT analysis
- **Restore its availability!**

Rule of five criteria

2 symptoms:
(paraesthesia)
2 Signs

test

1.investigation:

1. Leg pain > back pain
2. Specific neurological symptoms
3. SLR – 50% of normal
and/or crossover pain
and/or positive bowstring
4. Two of four neurological signs
5. Positive water soluble myelogram
And/or CT scan
And/or venogram

Spine
RANDOMIZED TRIAL
2013

Prospective Randomized Trial of Chemonucleolysis Compared With Surgery for Soft Disc Herniation With 1-Year, Intermediate, and Long-Term Outcome
Part II: The Radiological Outcome

Douglas Wardlaw, MB ChB, ChM, BSc, FRCSed,* Ian K. Ritchie, MB ChB, FRCSed, FRCSedOrtho,† Adel F. Sababheh, MB ChB, MChOrtho, FRCSed,‡ Mukta Vaidya, MD,§ Martin Downing, BSc,* and Clifford J. Eastmond, MD, FRCP, FRCP*†

- Loss of disc ht space same in both groups

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Other Agents

- Ziconotide
 - Toxin of the cone snail species *Conus magus*
 - Selective N-type voltage-gated calcium channel blocker
 - Intrathecal ONLY
- Tapentadol
 - Centrally acting opioid and norepinephrine reuptake inhibitor
- Vitamins
 - Vitamin E shown to be neuroprotective vs cisplatin
- Cannabinoids
 - MS
- Calcitonin

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Other Agents

- Baclofen
 - GABA B agonist
 - Spasticity
- Memantine
 - NMDA
 - Alzheimers
- Dextromethorphan
 - NMDA / opiate receptors
 - cough suppressant, pseudobulbar effects, dissociative hallucinogen
- Mexiletine
 - Na channel blocker Class 1A anti-arrhythmic

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The Future...

Ann Neurol. 2011 August ; 70(2): 207–212. doi:10.1002/ana.22446.

Gene Therapy for Pain: Results of a Phase I Clinical Trial

David J. Fink, M.D.¹, James Wechuck, Ph.D.³, Marina Mata, M.D.¹, Joseph C. Glorioso, Ph.D.², James Goss, Ph.D.³, David Krisky, M.D., Ph.D.³, and Darren Wolfe, Ph.D.³

- NP2 – replication defective HSV-based vector expressing human preproenkephalin (PENK)

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Inhibition of Nitric Oxide Mediated Protein Nitration: Therapeutic Implications in Experimental Radiculopathy.
DOI: 10.1097/BRS.0b013e3182a085d9
Spine 2014 in press

Lee, Seong Jae MD, PhD *; Kim, Tae Uk MD *; Park, Jeong-Soo PhD *; Ra, Jang Yun MD, PhD *
Miscellaneous

Works in both compressive and neuropathic models

View Abstract

AB Study Design. Experimental animal study Objective. This study investigated whether NO mediated protein nitration is involved in the pathogenesis of radiculopathy and whether the symptoms can be relieved by its suppression. Summary of Background Data. It has been reported that nitration of protein mediated by Nitric Oxide (NO) is involved in the degenerative neurologic disorders, but its involvement is not clear in the radiculopathy. Methods. Two kinds of rat models of radiculopathy were used. Radiculopathy was induced either by ligation of spinal nerve roots or transplantation of autologous nucleus pulposus (NP). In separate groups of rats, aminoguanidine (AG), a potent nitric oxide synthetase (NOS) inhibitor, was administered just before induction of radiculopathy, to suppress NO production and resultant nitration of protein. Sensation of the hind limb was evaluated by plantar stimulation test, and motor weakness was assessed by observation of gait pattern. Nitrotyrosine, product of protein nitration, was assayed quantitatively by Western immunoblotting. Results. Mechanical allodynia was observed in both compression and NP groups, but motor weakness was observed only in the compression group. Preoperative administration of AG attenuated mechanical allodynia and motor weakness. Optical densities of nitrotyrosine bands increased significantly in radiculopathy groups, but they were lowered by administration of AG. Conclusions. NO mediated protein nitration contributes to the development of both types of radiculopathies. Suppression of NO production can decrease protein nitration and relieve neural dysfunctions of radiculopathy. (C) 2013 by Lippincott Williams & Wilkins

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DISORDER TO HARMONY

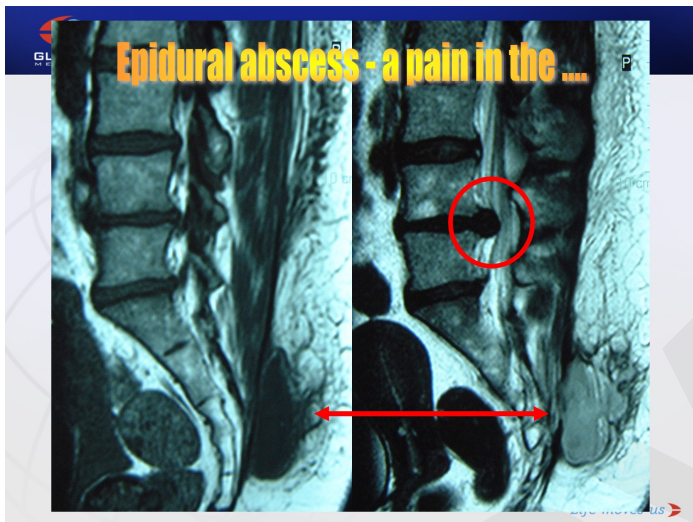
INFLAMMATION
ELIMINATE WHEAT
REDUCE GRAIN
LOW CARB
INCREASE OMEGA 3
FISH
FLAX NUTS
HEMP SEEDS
ELIMINATE PROCESSED / FRIED FOODS
INCREASE RAW GREEN JUICING
INCREASE FRESH PLANT PRODUCTS COLOUR-LEAVES, BERRIES
MICRONUTRIENT RICH FOODS ~ SEASONAL ORGANIC / WILD
FERMENT
DO NOTHING: FAST !!!
GARDEN YOUR GUT

DEPLETION
REDUCE STRESS
LEAVE LOVE
FEAR
CALM THOUGHTS
MEDITATION
EXERCISE
MOVE YOUR CHAI
BE IN NATURE
DO WHAT YOU LOVE

**"TURBO" BOOST: GREEN JUICE
SPIRULINA, SPROUTS, HEMP
VIT D'S, ASTAXANTHIN, VIT C
VIT E, MAGNESIUM, ZINC
TURNERIE, GINGER
GARLIC**

HARMONY

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Summary Pharmacological Options

- NSAIDs / COX2
- Opioids
 - Oxycodone, tramadol, fentanyl, morphine etc
- Antidepressants
 - TCAs – amitriptyline, nortriptyline etc.
 - SNRIs – duloxetine, venlafaxine etc.
- Anticonvulsants
 - Gabapentin, pregabalin, carbamazepine, valproate, lamotrigine, topiramate etc.
- Topical Agents
 - Lignocaine patch, capsaicin
- Epidural
 - Steroid, antiTNF α , clonidine, ketamine
- Intrathecal
 - Ziconotide, opioids

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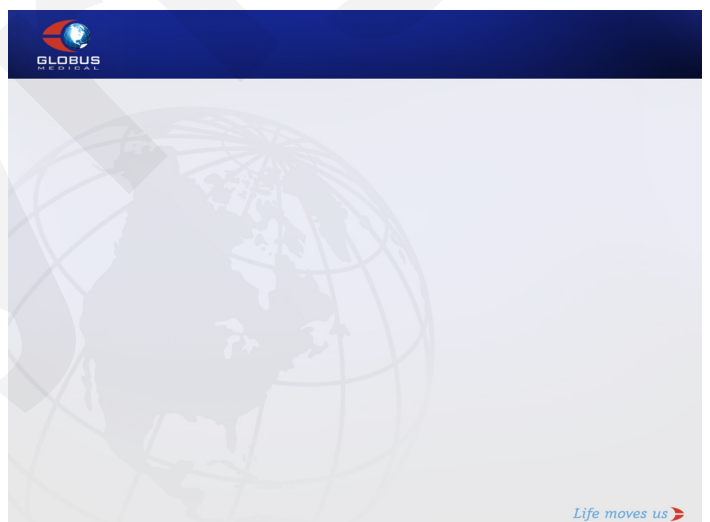
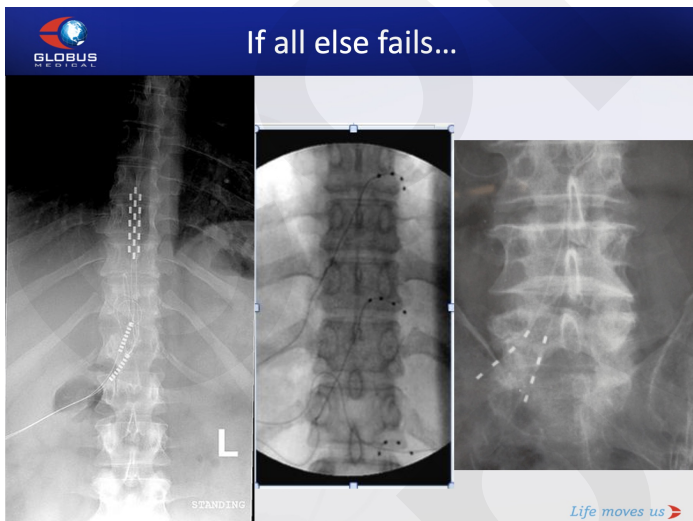
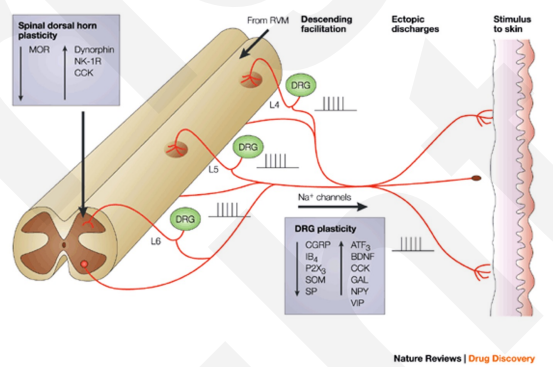


Table 7. Guidelines on Pharmacological Treatment of Neuropathic Pain

Pharmacological Treatment	
First Line for various conditions	Second Line
TCAs (25 to 150 mg/day)	Tramadol (200 to 400 mg/day)
Gabapentin (1200 to 3600 mg/day)	
Pregabalin (150 to 600 mg/day)	
First Line for restricted conditions	Second or Third Line
Lidocaine plaster (up to three plasters/day): PHN	Opioids
Duloxetine (60 to 120 mg/day): PDN	
Venlafaxine (150 to 225 mg/day): PDN	
Capsaicin 8% patch: PHN, HIV neuropathies	
Cannabinoids: MS	
Pregabalin SCI	
First Line for neuropathic cancer pain	
Gabapentin	
Tramadol, TCAs level B of evidence	
Combination therapy	
Gabapentin & TCAs	
Gabapentin & opioids	

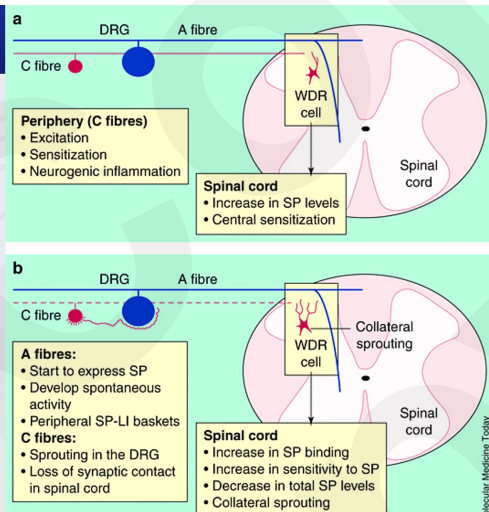
TCA, tricyclic antidepressants; PHN, post herpetic neuralgia; PDN, painful diabetic neuropathy; MS, multiple sclerosis; SCI, spinal cord injury; HIV, human immunodeficiency virus.

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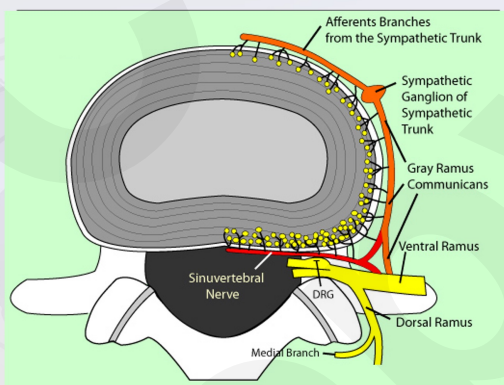


Nature Reviews | Drug Discovery

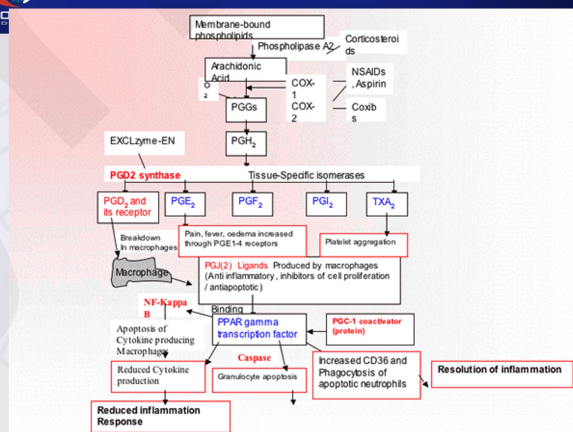
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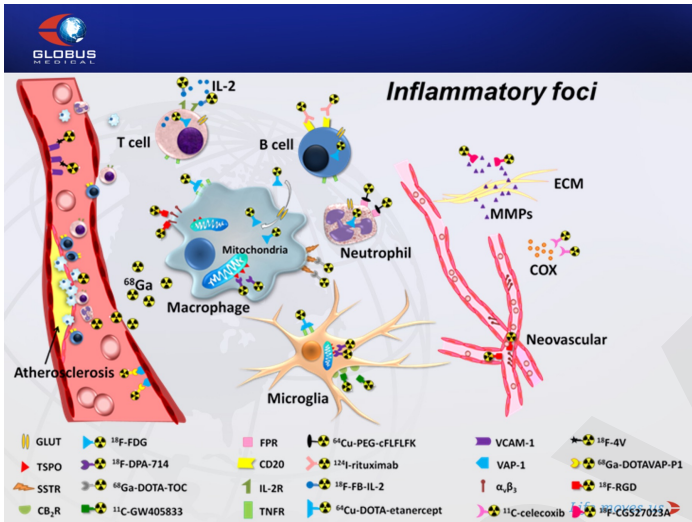
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PAIN[®]

PAIN[®] 150 (2010) 420-427

IASP

The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy

Ralf Baron^{a,*}, Rainer Freynhagen^b, Thomas R. Tölle^c, Christian Cloutier^d, Teresa Leon^e, T. Kevin Murphy^f, Ken Phillips^g, on behalf of the A0081007 Investigators

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Topical Agents: Proposed MOA

Drug	Mechanism
Lidocaine patch 5%	Acts by blocking sodium channels thereby reducing ectopic nerve impulses
Capsaicin	Acts via depletion of substance P and activity at the vanilloid receptor

MOA = mechanism of action.
Galer BS, et al. A Clinical Guide to Neuropathic Pain. McGraw-Hill Healthcare Companies; 2000:57-65.

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Opioids: Proposed MOA

Drug	Mechanism
Opioids	Modulates the perception of pain via the μ-opioid receptor ¹
Tramadol	Acts through both the μ-opioid receptor and inhibits the uptake of norepinephrine ²

1. Adriaenssen H, et al. Diabetes Metab Res Rev. 2005;21:231-240.
2. Raffa RB, et al. J Pharmacol Exp Ther. 1992;260:275-285.

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Antidepressants: Proposed MOA

Drug	Mechanism
TCAs	Inhibition of serotonin and norepinephrine reuptake
SNRIs	Inhibition of serotonin and norepinephrine reuptake

Adriaenssen H, et al. Diabetes Metab Res Rev. 2005;21:231-240.

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Anticonvulsants: Proposed MOA

Drug	Mechanism
Oxcarbazepine	Modulation of high-voltage activated calcium channels
Valproate, lamotrigine, topiramate, oxcarbazepine	Blockade of voltage-gated sodium channels
Gabapentin, pregabalin	Modulates voltage-gated Ca ²⁺ channels via binding to α ₂ -δ subunit of presynaptic neurons

Adriaenssen H, et al. Diabetes Metab Res Rev. 2005;21:231-240.

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Pharmacologic Treatments for Neuropathic Pain: Summary

Topicals

- Efficacy established in randomized controlled trials
- Application limitations

Opioids

- Efficacy established in randomized controlled trials
- Limitations: side effects are limiting; documentation and monitoring needed

Antidepressants

- Efficacy established in randomized controlled trials
- Limitations: adverse events limit usage, especially of TCAs
- Duloxetine
 - ≥50% reduction in pain reported by up to 50% of painful DPN patients
 - No evidence to support its use in PHN

Anticonvulsants

- Pregabalin
 - ≥50% reduction in pain reported by up to 48% of painful DPN patients
 - ≥50% reduction in pain reported by up to 50% of PHN patients
 - Rapid onset of action
 - Bid and tid dosing ranging from 300-600 mg/d