
ALLEVIO
PAIN MANAGEMENT

Disclosures

I have no relevant financial interest/arrangement or affiliation with any organizations related to commercial products or services to be discussed at this program

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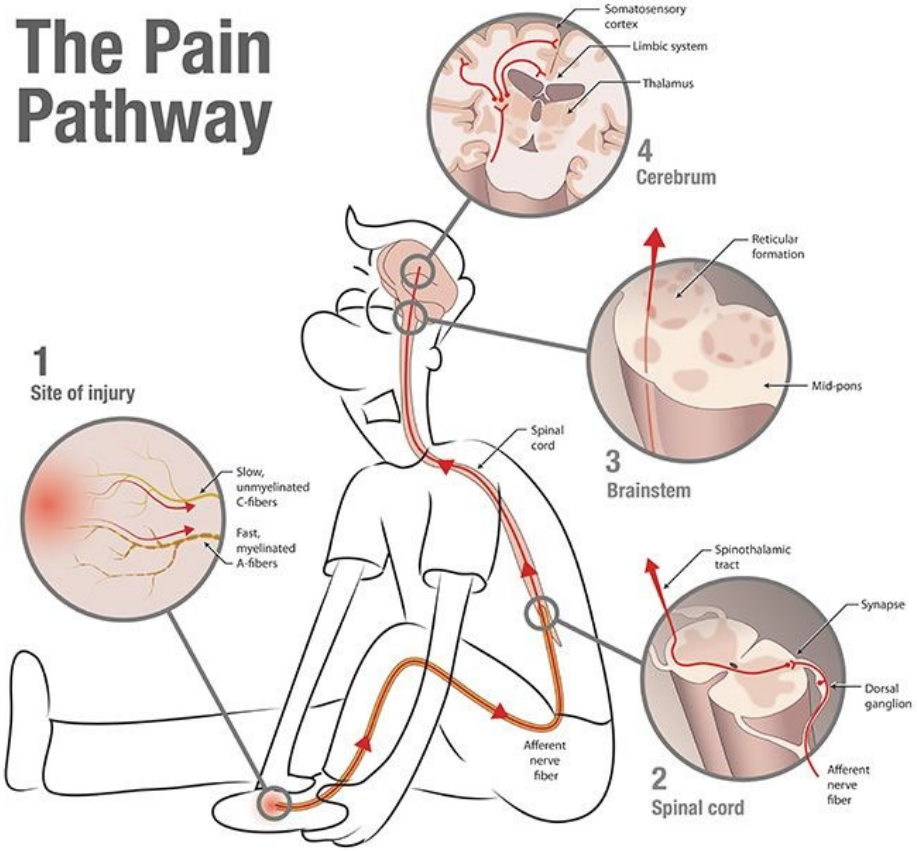
Objectives

1. Definition of Pain
2. Pain Pathways
3. Understand Basis of Nociceptive and Neuropathic pain

IASP definition of pain

- International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

The Pain Pathway



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- Both acute and chronic pain are an enormous problem in the United States, costing 650 million lost workdays and $65 billion a year.
- **Acute pain**:
  - Provoked by a specific disease or injury
  - Serves a useful biologic purpose
  - Associated with skeletal muscle spasm and sympathetic nervous system activation
  - Self-limited.
  - Treatment aimed at treating the underlying cause and interrupting the nociceptive signals.
- **Chronic pain**:
  - May be considered a disease state
  - Outlasts the normal time of healing, if associated with a disease or injury
  - May arise from psychological states
  - Serves no biologic purpose
  - Has no recognizable end-point
  - Treatment must rely on a multidisciplinary approach and should involve more than one therapeutic modality

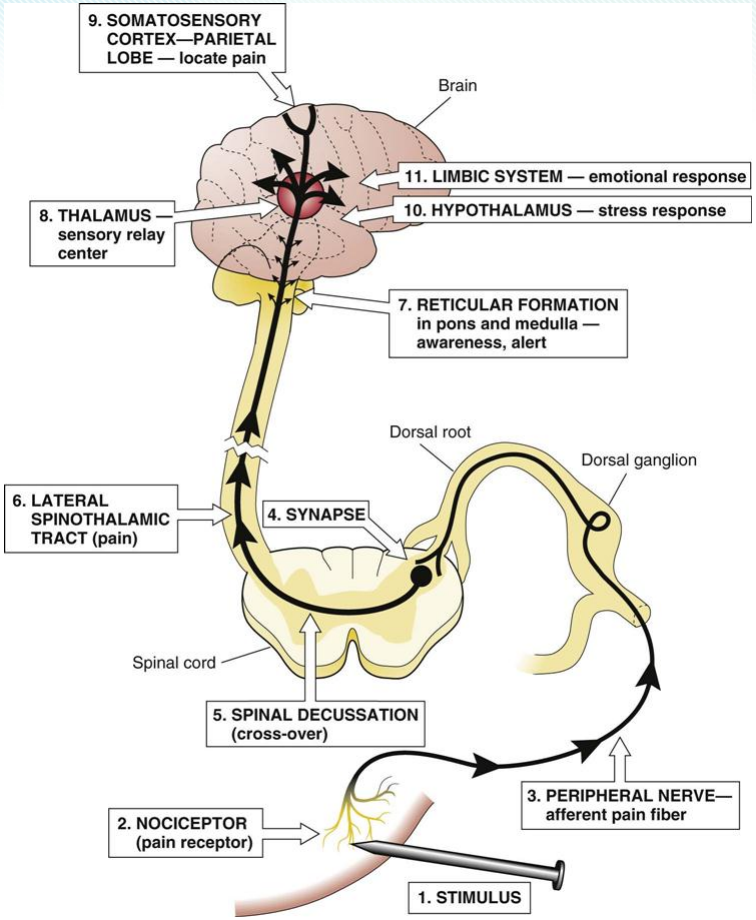
- Nociceptive pain:
  - experienced by everyone suffering any kind of injury or localized inflammatory process.
  - activation of small diameter afferent nerve fibers
- Aδ fibers -“Fast pain fibers” are lightly myelinated
  - relay a sharp, stinging sensation to nociceptive-specific neurons located at the margin of the dorsal horn.
  - responsible for alerting to the presence of pain but not necessarily transmitting its intensity.
- C-fibers - Smaller diameter (slower) nerve fibers
  - rely aching, burning type pain.
  - responsible for relaying the intensity of the pain.
  - poorly localized in the nervous system since it is transmitted to higher centers by neurons in the dorsal horn that receive widely convergent input.

- Several levels of the nervous system
- Notably the dorsal horn of the spinal cord and the thalamus
- These are mechanisms for filtering the signal.
- Therefore activation of a few nociceptive fibers along with a large number of touch nerve fibers is unlikely to be experienced as pain.
- Treatment of nociceptive pain requires resolution conditions activating nociceptive fibers.
  - For example, if local inflammation is a major factor, suppression of the inflammatory reaction would be expected to resolve the pain.

- **Neuropathic pain**:
  - Fundamentally different from nociceptive pain.
  - Generated or sustained by the nervous system.
  - Either peripheral or central nervous systems.
  - In the central nervous system, there may be reorganization of the pathways that transmit the signal or the functions of systems that normally filter or suppress pain.
  - Central and peripheral factors may combine to contribute to the genesis of neuropathic pain syndromes.
  - Regardless of whether peripheral or central processes predominate, neuropathic pain responds poorly to normal pain treatments.

- Neuropathic pain is, by definition, chronic and may escalate with time.
  - This is as opposed to most acute, nociceptive pain problems that lesson with time and with healing.
- Neuropathic pain may augment associated with some structural or physiological changes in neurons of the pain pathways.
  - Neuropathic conditions include diabetic neuropathy, postherpetic neuralgia, phantom limb pain, deafferntation and trigeminal neuralgia.
  - The mechanisms responsible for neuropathic pain in these conditions are relatively well understood
  - Other conditions, such as trauma and other orthopedic problems, are less commonly understood triggers.

- Mechanisms for generation of neuropathic pain, some affect peripheral and some affect central nervous system function.
- In the peripheral nervous system, main mechanisms:
  - 1. Disorders that result in spontaneous firing of damaged nerve fibers
  - 2. Processes that result in oversensitivity of afferent pathways due to denervation
  - 3. Sympathetically maintained pain.
- In the central nervous system:
  - Sensitization at the synaptic level or through reorganization of higher processing mechanisms.



- ***Peripheral neuropathic pain***
- Oversensitivity and spontaneous activity of damaged fibers can occur with directly injured nociceptive nerve fibers.
- At the site of injury there is increased ion channels and insertion of additional types of receptors into the neuronal membrane.
  - This process can result in sensitization of the nerve fiber to both mechanical and chemical mediators.
- Several well-known clinical conditions, such as trigeminal neuralgia, radiculopathy, plexopathies and certain compression injuries in nerves, can result in this type of sensitization.
  - These conditions result in projected pain, with pain being felt very specifically along the distribution of the peripheral sensory nerve fibers.
- Initial treatment for this type of neuropathic pain should be directed at the mechanical and chemical factors at the site of damage
- These changes may be chronic and resistant to improvement

- For example, there may be ectopic foci of firing along and damaged nerve fiber.
- This type of pain is often described as shooting or stabbing and, when many nerve
- Fibers are firing asynchronously, the pain may be described as a continuous burning pain.
- This is a process that can produce pain in an anesthetic part of the body (anesthesia dolorosa)
- Often larger fibers may be completely absent, resulting in overall decrease in sensitivity
- Persistence of C-fibers can result in magnification of pain due to spontaneous firing.
- Treatments directed at stabilizing oversensitive nerve membranes, including anesthetics and anticonvulsant medications

- **Deafferentation pain**
- Results from the interruption of sensory conduction due to damage to large diameter sensory nerve fibers
  - The ones that mediate touch and pressure sense
- Increase sensitivity and irritability of neurons further along the sensory pathway.
- Loss of competition between the large-diameter “normal” sensory input and input from small diameter, nociceptive fibers.
  - Magnifies the transmission and the perception of pain.
  - Same way a sound heard louder in an otherwise silent room.
- Chronic lack of normal sensory input decreases number of inhibitory neurons in second and third order nuclei of the central nervous system
  - Presumed through transynaptic degeneration
- Result in spontaneous firing of second and third order neurons.
- Pain occurs in the area of diminished or even completely lost sensation.

- **Complex regional pain syndrome**
- Several names in the past
  - complex regional pain, reflex sympathetic dystrophy, causalgia or sympathetically maintained pain
- Variability in triggers and in presentation.
- Irregularities in autonomic nervous system function
  - changes in circulation and temperature
  - changes in sweating patterns
  - neurogenic inflammation
- Sympathetic nerve fibers not only secrete norepinephrine, but also certain inflammatory mediators such as prostaglandins and certain nerve growth factors.
  - Stimulate small diameter nociceptive fibers directly and may sensitize them
  - Particularly when nociceptive fibers have been damaged.

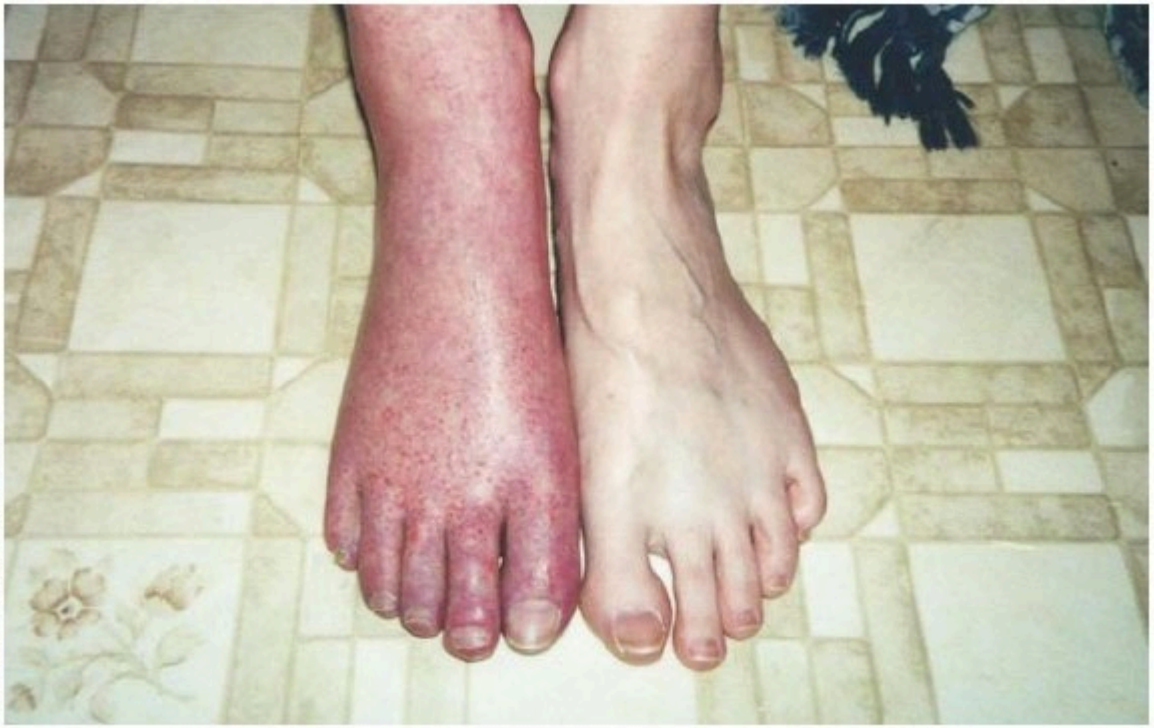


Photo courtesy of Dr. Steven Richelmer.

Figure 1. Image of a patient with lower extremity complex regional pain syndrome.

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- Release of inflammatory mediators along with sympathetic neurotransmitters.
  - These factors interact with tissue elements
  - Inflammation must be considered to be a complex interaction between tissue components and the nervous system
- Neurotransmitters released from sensory nerve fibers in the periphery can also contribute to the inflammatory reaction.
- These neurotransmitters sensitize other pain fibers
  - Result in vasodilation, edema, infiltration of white blood cells and activation of other inflammatory cells.
- Nervous system not a passive participant in inflammation, but rather a pivotal factor in magnifying and sustaining inflammation.
  - This why conditions that activate sensory nerve fibers and the sympathetic nervous system can aggravate local inflammation.
- Also certain types of nerve blocks may be effective in abolishing chronic pain.
  - Chronic application of capsaicin
    - Depletes the number of small pain fibers in an area
    - Diminish this component of the inflammatory reaction.

- Neurogenic inflammation may be central in many chronic pain conditions.
  - True causalgia
    - Sustained pain and autonomic changes due to damage to nerve trunks.
  - Other types of sympathetically maintained pain
    - Differences in the specific tissues that neurogenic inflammation acting on.
- Treatment of complex regional pain syndrome is difficult and sometimes frustrating.
- Early in the condition aggressive mobilization, and physiotherapy is helpful.
- Active exercises are better tolerated than passive, since there is often cutaneous hyperesthesia.
  - Various methods of pain control, to enhance the patient's tolerance for movement-related therapies.
- The mechanism whereby mobilization helps the condition is not clearly understood
  - May involve low-frequency activation of normal sensory fibers that are known to promote long-term depression of synaptic transmission in overactive pain pathways

Thank You

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Multidisciplinary approaches to pain management

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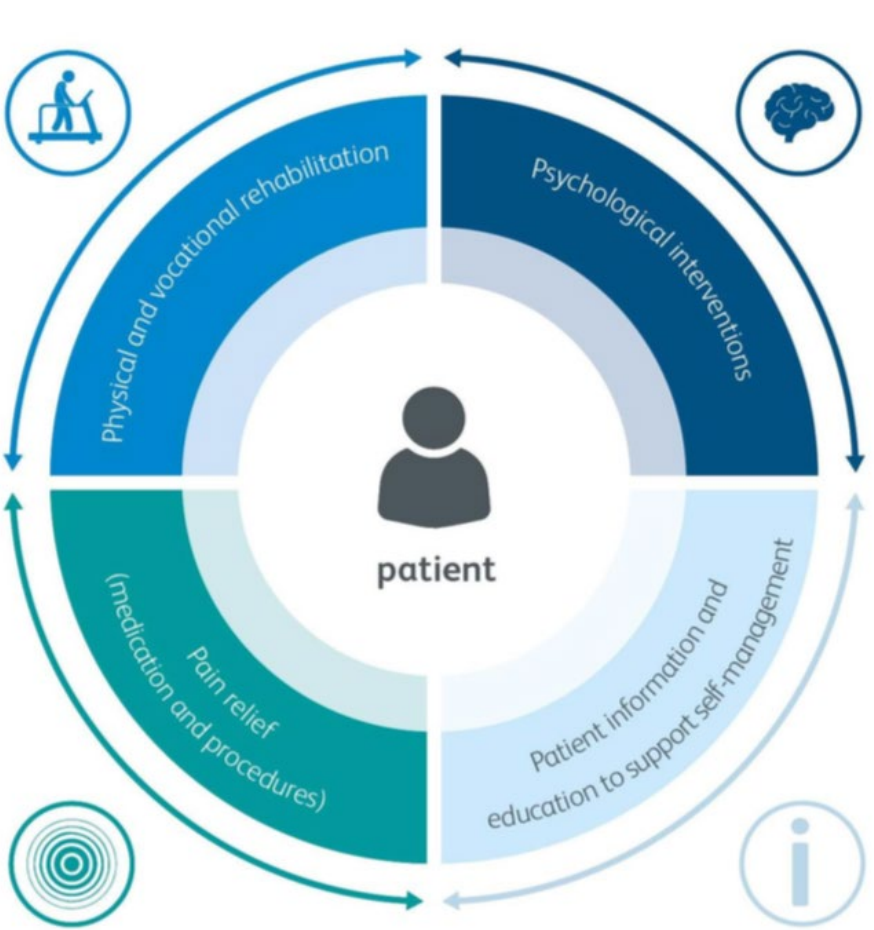
Objectives

- Biopsychosocial management
- Comprehensive Pain Assessment
- Tools to aid assessment
- Monitor progress and Treatment outcomes
- Current Evidence based medicine for common pain conditions

Four Pillars of Treatment for chronic pain conditions



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- Appreciate that there are significant individual differences in pain experience and pain responses.
- Understand that social and psychological factors act in association with biological factors to influence an individual's pain experience and pain behaviours in both acute and chronic pain.
- Understand that describing pain as 'psychological', 'psychogenic', or 'psychosomatic' may be stigmatising and fails to take sufficient account of the complex biopsychosocial mechanisms that underlie all pains.
- Know that the psychological influences on pain experience include the person's behavioural responses, thoughts and beliefs as well as emotional factors and attentional processes
- Understand that psychological factors can be shaped by the individual's past experiences and by social influences: e.g. via the family and the wider culture
- Understand that individuals may employ a wide range of coping strategies to avoid and reduce pain and appreciate that, while some strategies may be adaptive, others may be maladaptive

  directly or indirectly impacting upon mood, identity and self-esteem, social roles and responsibilities, hobbies and leisure activities, and occupational and financial circumstances

Importance of recognizing psychosocial factors in pain

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Pain Assessment

- Pain cannot be adequately managed if its impact is not assessed regularly using valid and reliable tools.
- Understand that, because pain is a subjective experience, the most appropriate way to assess it is through self-report.
- Conduct a comprehensive assessment of the individual's pain-associated disability and distress, including their activities of daily living, fitness, function and mood.
- Act on this assessment appropriately, based on best available evidence.
- identify groups where verbal reporting of pain may be restricted, including children and those with cognitive impairment or learning disabilities, and be aware of alternative forms of assessment.

Communication

- Assess an individual's understanding of pain and their treatment options and identify myths, fears and misconceptions that may act as barriers to effective management
- Use a person-centred perspective to formulate appropriate treatment plans
- Discuss and explain the evidence underpinning commonly used pain management approaches in appropriate
- language to enable the individual with pain to make informed choices
- Recognise the roles of the members of the interprofessional team dealing with pain and be able to communicate effectively
- Recognise the contribution of family, carers, voluntary and support groups/agencies in supporting people with pain and be able to communicate effectively.

Patient journey to 1st encounter at Allevio pain management

- Referral from Family physician or specialist
- Referral triaged for:
  - Completeness
  - Appropriate for community setting or knowledge and skills of Practioner's
  - Urgency e.g acute radiculopathy, post surgical pain, CRPS
- Two weeks before appointment – link sent to fill out validated questionnaires specific to there pain complaint using Ocean system.
- 1st consult – comprehensive pain assessment and collaborate with patient and agree management plans with the person affected by pain and their carers/family.
- Devise appropriate comprehensive treatment plans including pharmacological, physical, psychological and complementary approaches.

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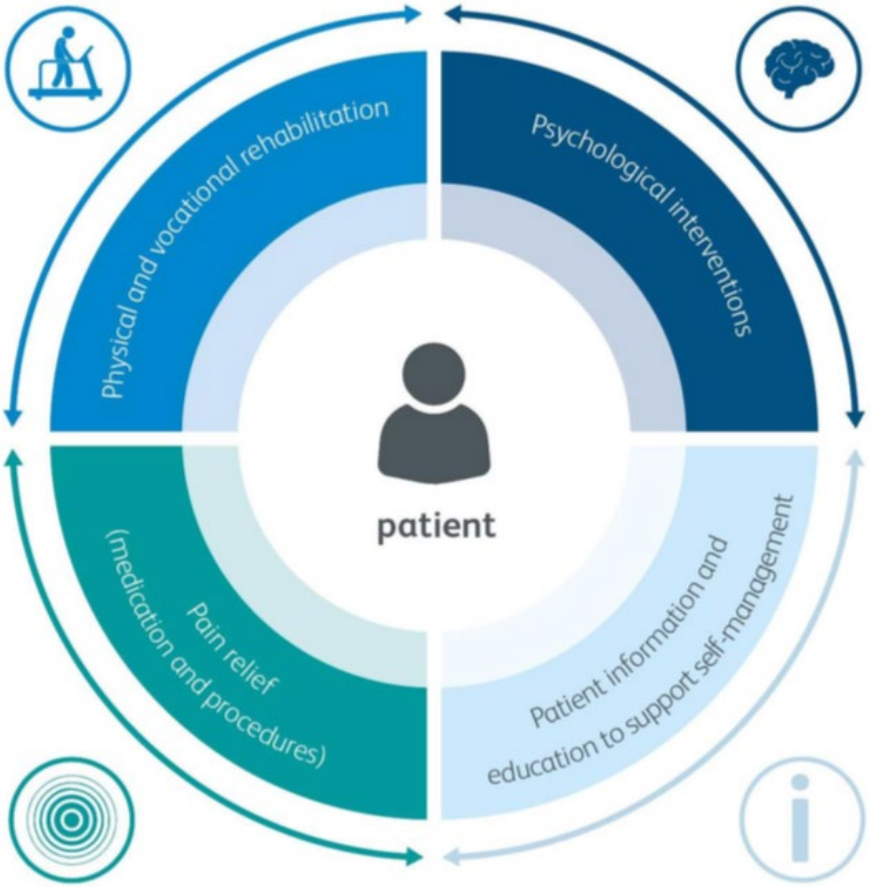
Four Pillars of Treatment for chronic pain conditions



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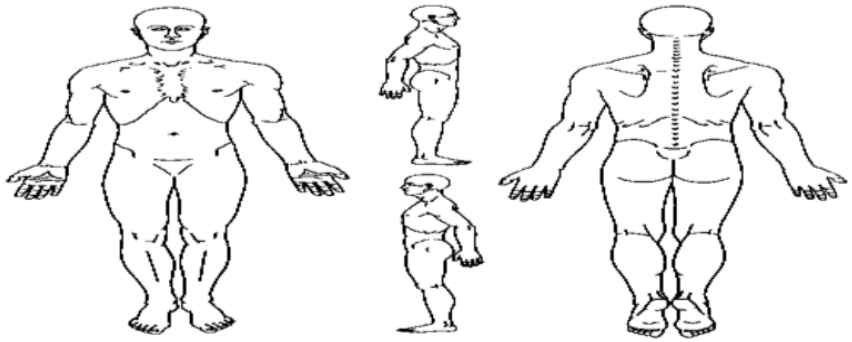
Assessment of Pain

Patient Questionnaire & Ocean

- Back pain
- Neck pain
- Widespread body pain
- headache
- Neuropathic pain
- Post surgical pain

Location of pain: please mark an "X" on the drawings where you feel the WORST pain(s).



0 = Does not interfere 10 = Completely interferes

General Activity	0	1	2	3	4	5	6	7	8	9	10
Mood	0	1	2	3	4	5	6	7	8	9	10
Walking ability	0	1	2	3	4	5	6	7	8	9	10
Normal work	0	1	2	3	4	5	6	7	8	9	10
Relations with other s	0	1	2	3	4	5	6	7	8	9	10
Sleep	0	1	2	3	4	5	6	7	8	9	10
Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

Ocean Questionnaire for Low back Pain Disability

Oswestry Low Back Pain Disability Questionnaire

Instructions

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. We realize you may consider that two or more statements in any one section apply but please just indicate the statement which most clearly describes your problem.

Section 1 - Pain intensity:

Please rate the intensity of your pain at this moment

Section 2 - Personal care (washing, dressing etc):

Please describe your personal care

Section 3 - Lifting:

Please describe your experience with lifting

Section 4 - Walking:

Please describe your walking habits

Section 5 - Sitting:

Please describe your sitting habits

Section 6 - Standing:

Please describe your standing habits

Section 7 - Sleeping:

Please describe your sleeping habits

Section 8 - Sex life (if applicable):

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For how many years have you had symptoms of fibromyalgia?

How many years ago were you diagnosed with fibromyalgia?

In the past week, were you able to:

1. Do shopping?	Always	Most	Occasionally	Never	Not Applicable
2. Do laundry with a washer and dryer?	Always	Most	Occasionally	Never	Not Applicable
3. Prepare meals?	Always	Most	Occasionally	Never	Not Applicable
4. Wash dishes / cooking utensils by hand?	Always	Most	Occasionally	Never	Not Applicable
5. Vacuum a rug?	Always	Most	Occasionally	Never	Not Applicable
6. Make beds?	Always	Most	Occasionally	Never	Not Applicable
7. Walk several blocks?	Always	Most	Occasionally	Never	Not Applicable
8. Visit friends or relatives?	Always	Most	Occasionally	Never	Not Applicable
9. Do yard work?	Always	Most	Occasionally	Never	Not Applicable
10. Drive a car?	Always	Most	Occasionally	Never	Not Applicable
11. Climb stairs?	Always	Most	Occasionally	Never	Not Applicable

Of the 7 days in the past week:

12. How many days did you feel good?	0	1	2	3	4	5	6	7

Fibromyalgia Impact Questionnaire

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Headache Impact Test (HIT-6)

Please select one answer for each question.

1. When you have headaches, how often is the pain severe?

Never | Rarely | Sometimes | Very often | Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never | Rarely | Sometimes | Very often | Always

3. When you have a headache, how often do you wish you could lie down?

Never | Rarely | Sometimes | Very often | Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never | Rarely | Sometimes | Very often | Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never | Rarely | Sometimes | Very often | Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never | Rarely | Sometimes | Very often | Always

Headache Impact Questionnaire

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Assessment of Pain

- **Medical History**
  - ➢Onset and Duration
    - Acute pain <6 months
    - Chronic pain >6 months
  - ➢Location
  - ➢Radiation
  - ➢Aggravating and relieving factors
  - ➢Description

◯ shooting ◯ sharp ◯ stabbing ◯ throbbing ◯ aching ◯ heavy ◯ tight ◯ burning

◯ cramping ◯ numbness, where? _____ ◯ pins/needles ◯ tingling

◯ shooting pain down the ◯ right ◯ left ◯ arm ◯ leg

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Assessment of Pain

- Past medical and surgical history
- **Social and Psychological History**
- **Functional impairment and sleep disruption**
- **Physical Examination**

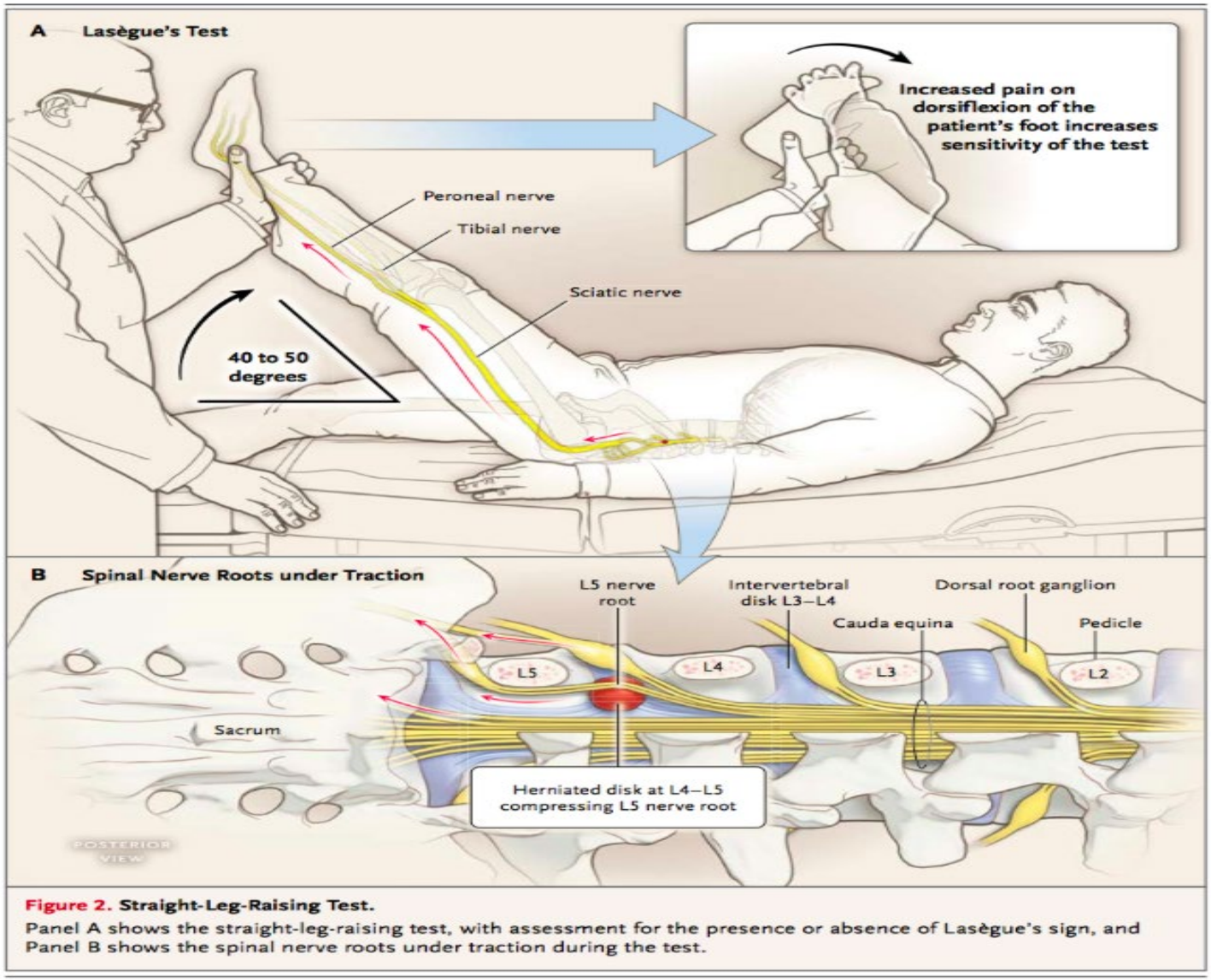

Figure 2. Straight-Leg-Raising Test.

Panel A shows the straight-leg-raising test, with assessment for the presence or absence of Lasègue's sign, and Panel B shows the spinal nerve roots under traction during the test.

Assessment of Pain – *Red Flags*

	Diagnosis of Concern			
Findings	**Fracture**	**Cancer**	**Infection**	**Cauda Equina**
Age >50 years	★	★		
Fever, Chills, recent urinary tract infection			★	
Unintended weight loss		★		
Significant trauma	★			
History of Cancer		★		
I.V Drug abuse			★	
Progressive motor or sensory deficit		★		★
Prolonged use of corticosteroids	★		★	
History of Osteoporosis	★			

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Diagnosis

- ❑Differential Diagnosis
- ❑Order Lab Tests if appropriate
- ❑Radiological Investigations
- ❑Treatment Plan

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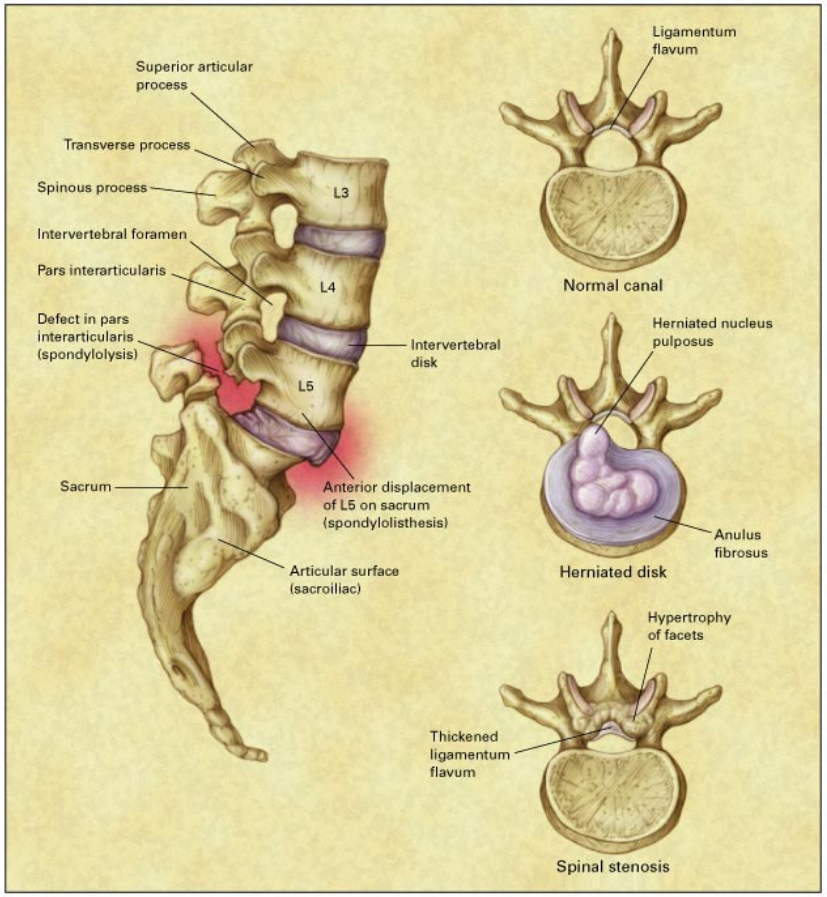
Common Pathoanatomical Conditions of the Lumbar Spine



Deyo R and Weinstein J. N Engl J Med 2001;344:363-370

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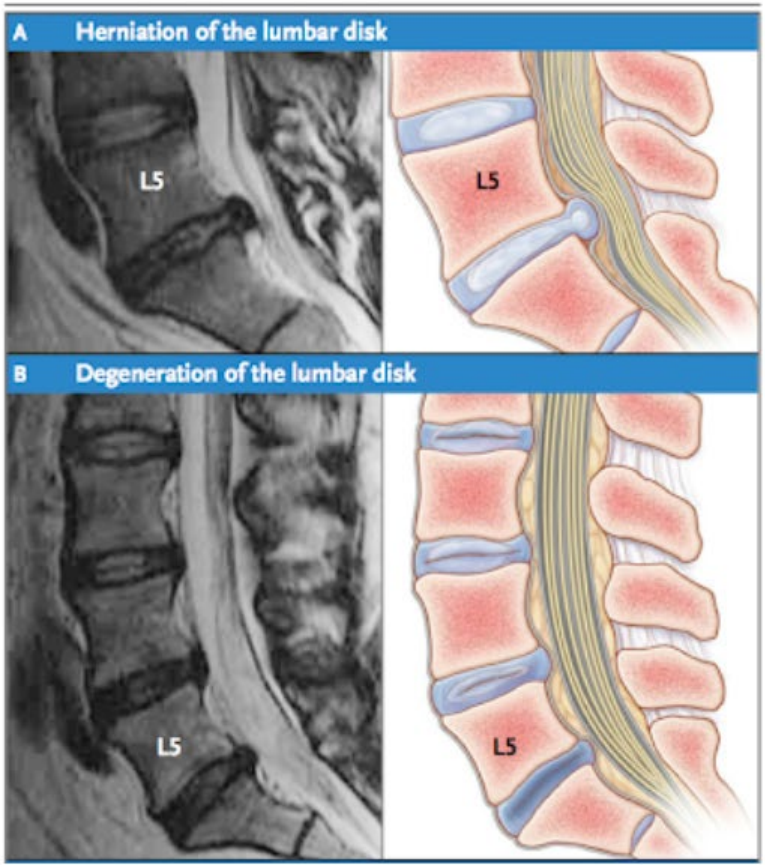
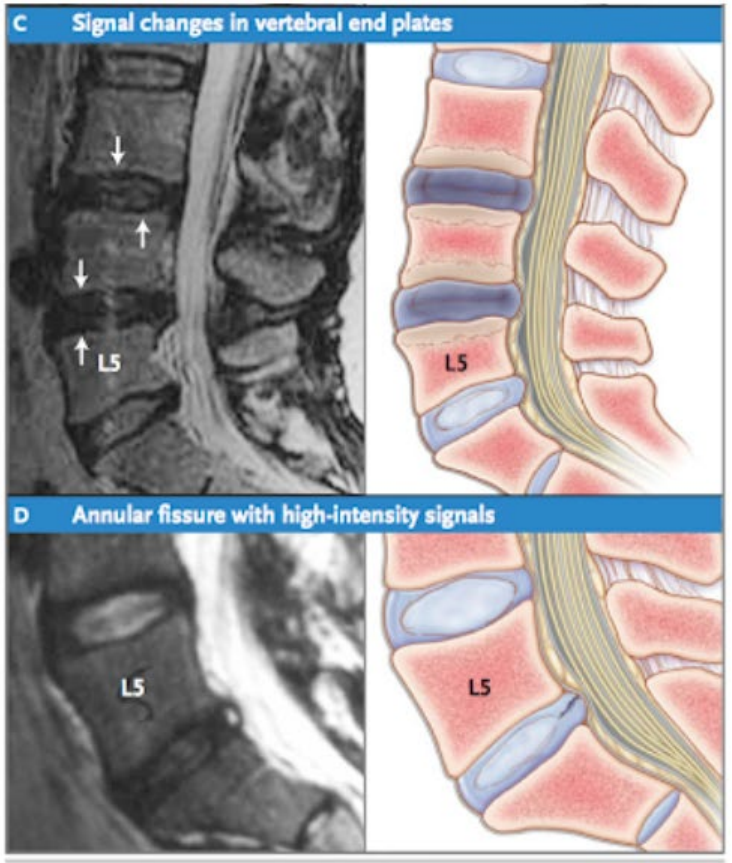
Persistent Low Back Pain





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For example - Differential Diagnosis – Back Pain (can also be used for neck pain pain)

Disease/Condition	Differentiating Signs/Symptoms	Differentiating Tests
Lumbar strain or sprain (≥70%)	Diffuse pain to lumbar muscles; some radiation to buttocks	• Facet loading • Faber Test • SLT
Degenerative Disc or facet process	Localized Lumber pain; similar to lumbar strain Can also present with patchy leg symptoms	• Facet loading • Neuro test
Spinal compression fracture	Spine tenderness on palpation, particularly in older patients with a history of steroid treatment and/or osteoporosis.	• Lumbosacral x-ray can show fractures. • Spine CT can more clearly define bony pathology.
Radiculopathy/sciatica	Numbness, weakness in lower extremities, pain radiating to buttock and leg (especially if the pain radiates beyond the knees). Radiculopathy/sciatica is often unilateral	• Abnormal or asymmetric patellar, hamstring, or ankle reflex. • Positive straight-leg raise test. • Lumbar MRI or myelography • Lumbar CT • EMG
Spinal Stenosis	Numbness, weakness in lower extremities, pain radiating to buttock and leg, and neurogenic claudication	• Lumbar MRI • Lumbar CT, • Myelography

Pain Relief – Medications and Procedures

Pharmacologic management

Acetaminophen

NSAIDs

Opioids

Neuropathic pain meds (antidepressants, anticonvulsants)

Chronic Pain Managment

Comprehensive evaluations

Epidural steroid injections

Spinal injections

Radiofrequency facet neurotomy

Lidocaine/Ketamine infusions

Back pain differential diagnosis algorithm

➢ **Facet Testing**

= Radiofrequency Facet Neurotomy

- Back pain with radiculopathy

➢ **SI Joint Testing**

= Radiofrequency Facet Neurotomy

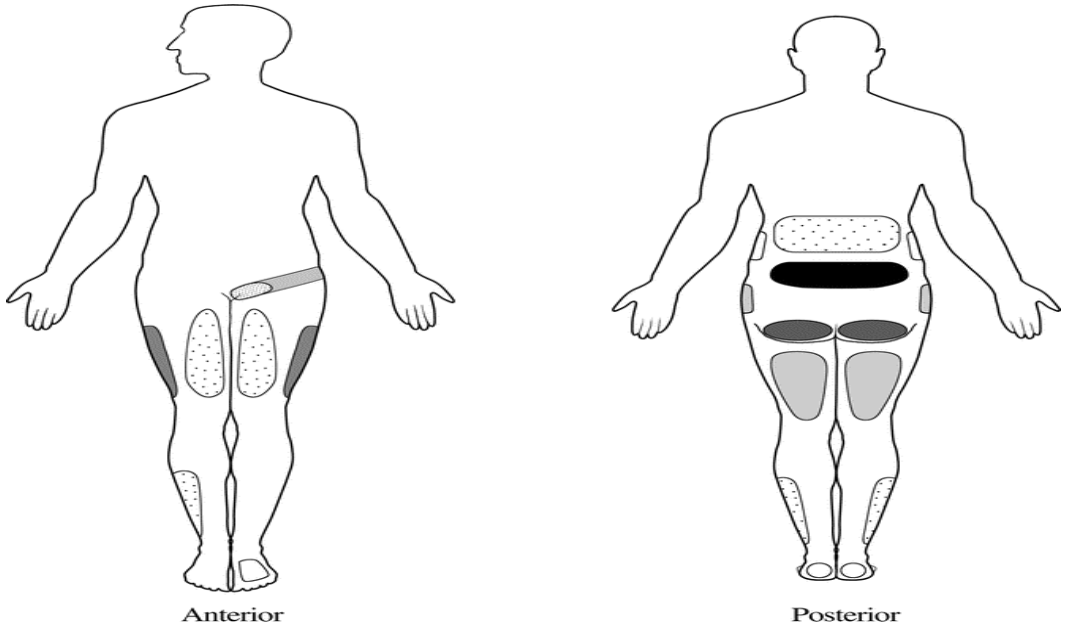
➢ **Disc Testing**

= Discography/ L2 dorsal root ganglion testing
= PRP / Stem Cell Therapy

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

From: Pathogenesis, Diagnosis, and Treatment of Lumbar Zygapophysial (Facet) Joint Pain
Anesthes. 2007;106(3):591-614.

Lumbar Facet pain patterns



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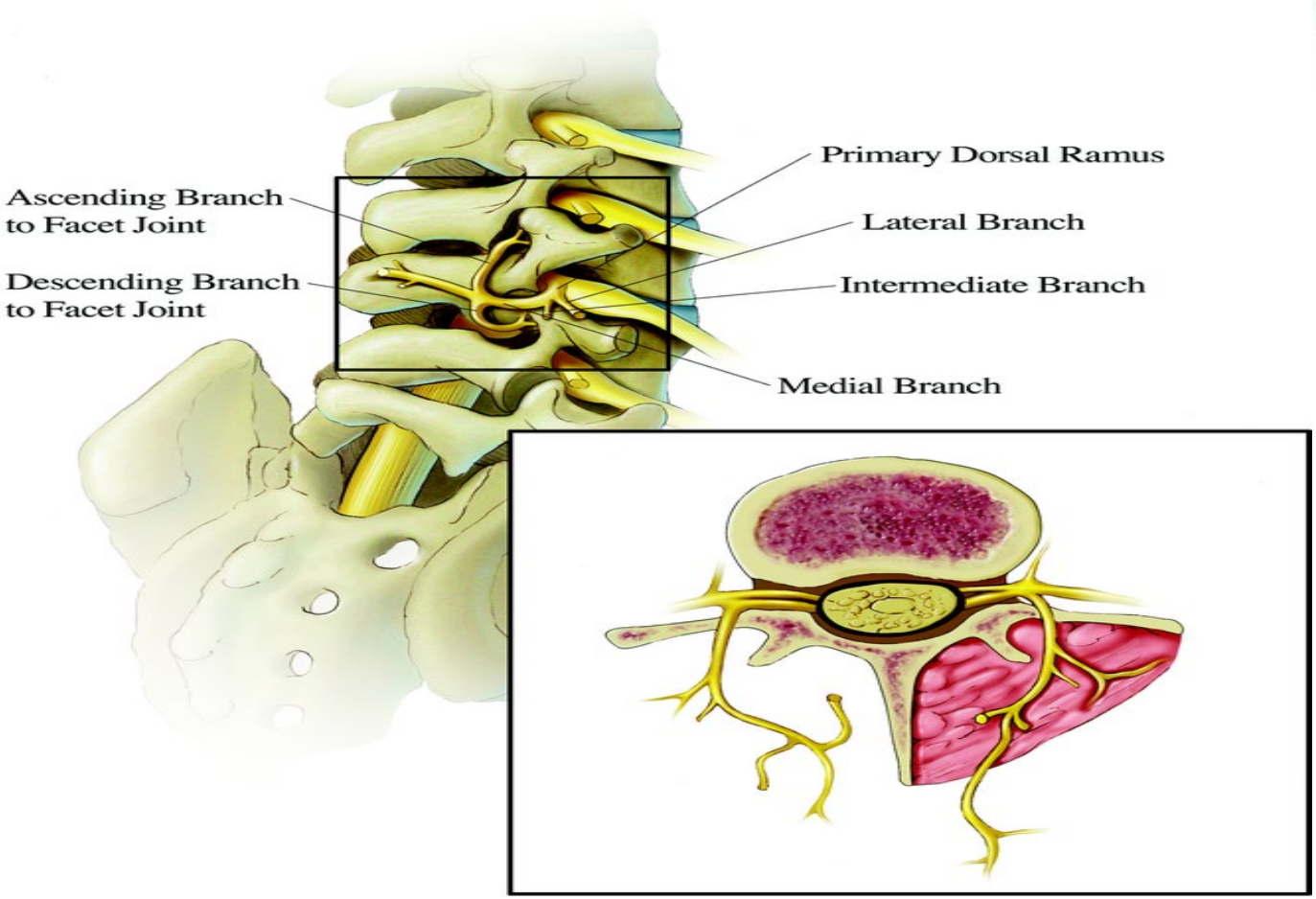

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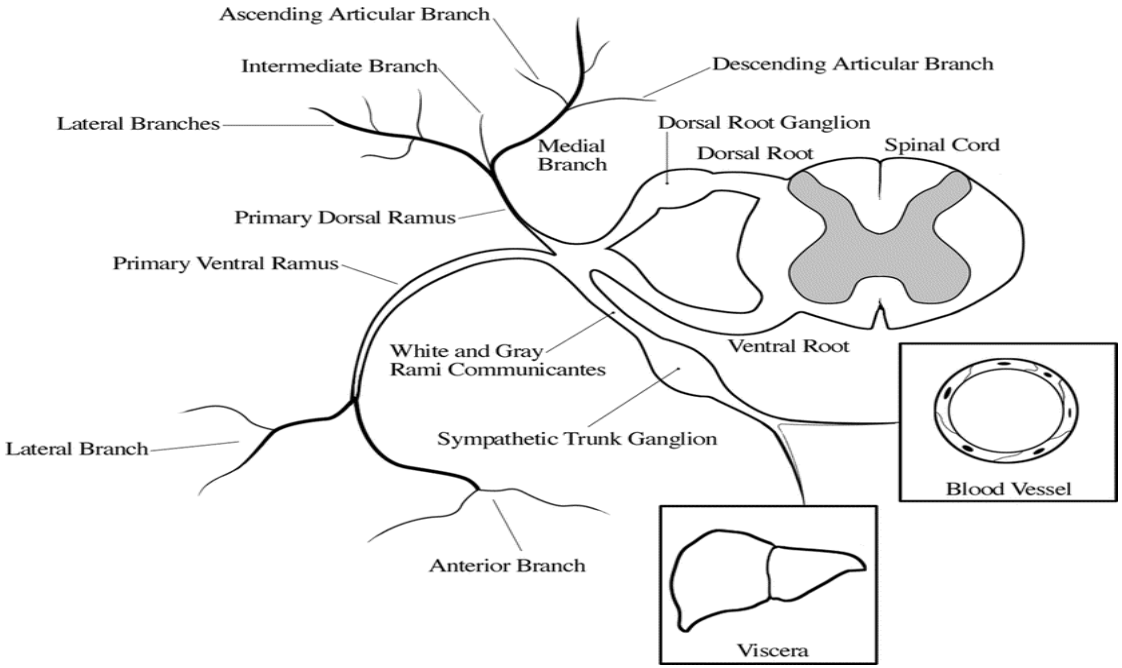
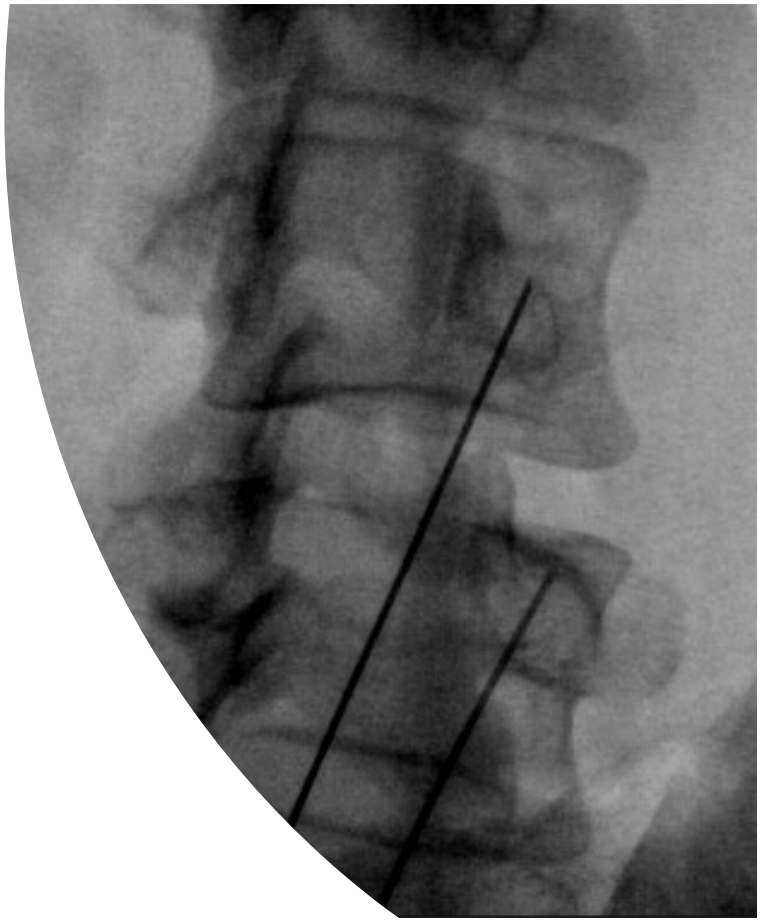


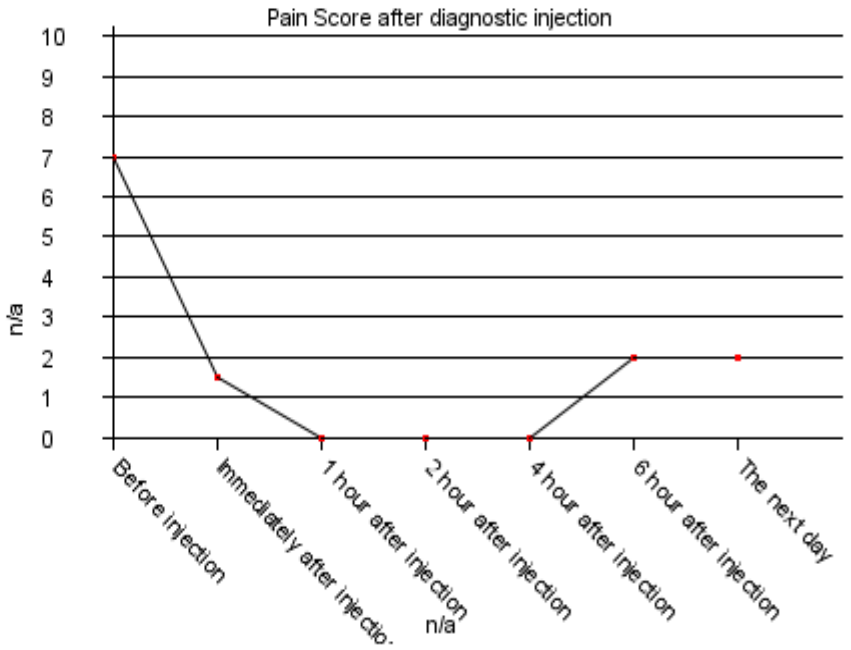
Medial Branch Block



The following pain scores were reported by the patient following the diagnostic procedure.

Test Medication:

Pain Score	Time
7	Before injection
1.5	Immediately after injection
0	1 hour after injection
0	2 hour after injection
0	4 hour after injection
2	6 hour after injection
2	The next day
	Click to finish the graph



Pain Score Results

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Radiofrequency ablation for chronic low back pain: A systematic review of randomized controlled trials

LE Leggett | LJJ Soril | DL Lorenzetti | T Noseworthy | R Steadman | S Tiwana

OBJECTIVE: To determine the efficacy of RFA for chronic low back pain associated with lumbar facet joints, sacroiliac joints, discogenic low back pain and the coccyx.

METHODS: A systematic review. Medline, EMBASE, PubMed, SPORTDiscus, CINAHL and the Cochrane Library were searched up to August 2013 Included articles were sham-controlled randomized controlled trials (RCTs), assessed the efficacy of RFA, reported at least one month of follow-up and included participants who had experienced back pain for at least three months.

RESULTS: 11 sham-controlled RCTs were included: 3 studies involving discogenic back pain; 6 studies involving lumbar facet joint pain; and two studies involving sacroiliac joint pain. The evidence supports RFA as an efficacious treatment for lumbar facet joint and sacroiliac joint pain, with five of six and both of the RCTs demonstrating statistically significant pain reductions, respectively. The evidence supporting RFA for the treatment of discogenic pain is mixed.

THE PREVALENCE OF CHRONIC CERVICAL ZYGAPOPHYSEAL JOINT PAIN AFTER WHIPLASH

Barnsley, Lord, Wallis & Bogduk
Spine V20, N1 pg 20-24, 1995

On the basis of medial branch (facet joint nerve) blocks, the prevalence of cervical facet joint pain is estimated at 40-55% in patients with post traumatic chronic neck pain (whiplash) .

Cervical facet referred pain patterns

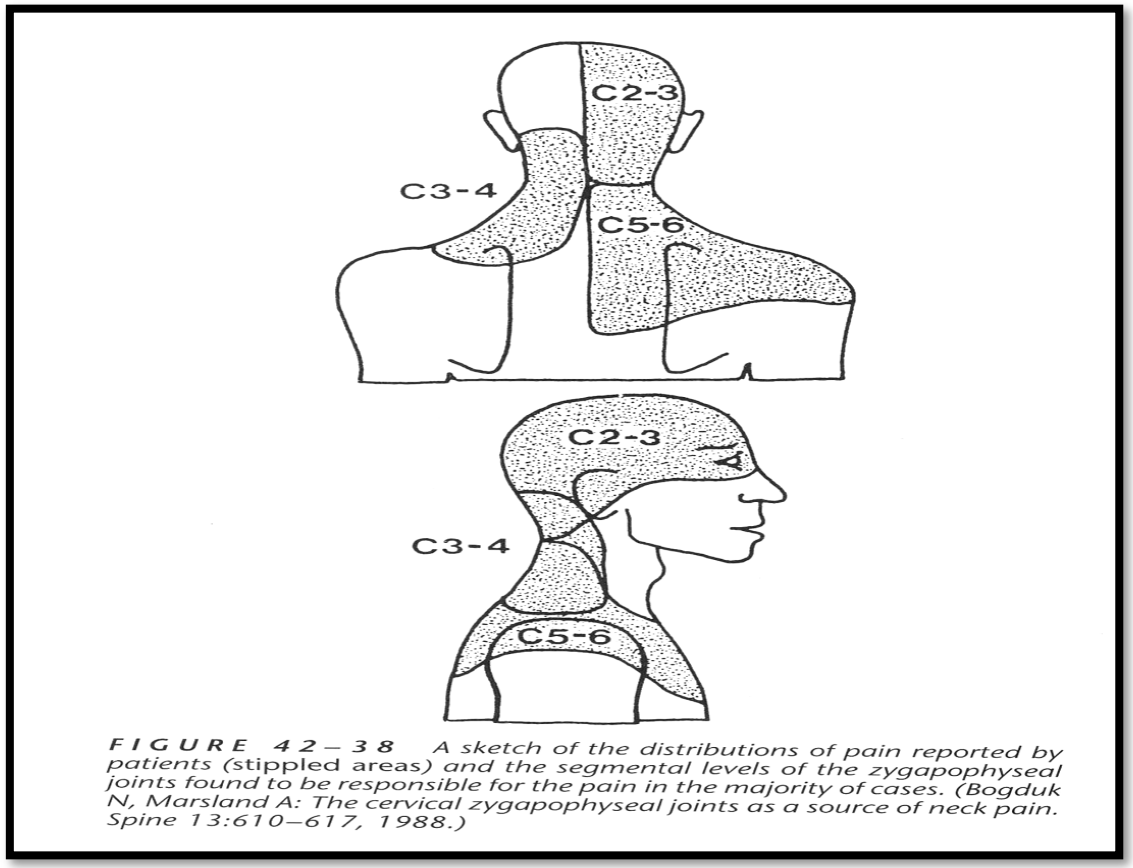


FIGURE 42–38 A sketch of the distributions of pain reported by patients (stippled areas) and the segmental levels of the zygapophyseal joints found to be responsible for the pain in the majority of cases. (Bogduk N, Marsland A: The cervical zygapophyseal joints as a source of neck pain. Spine 13:610–617, 1988.)

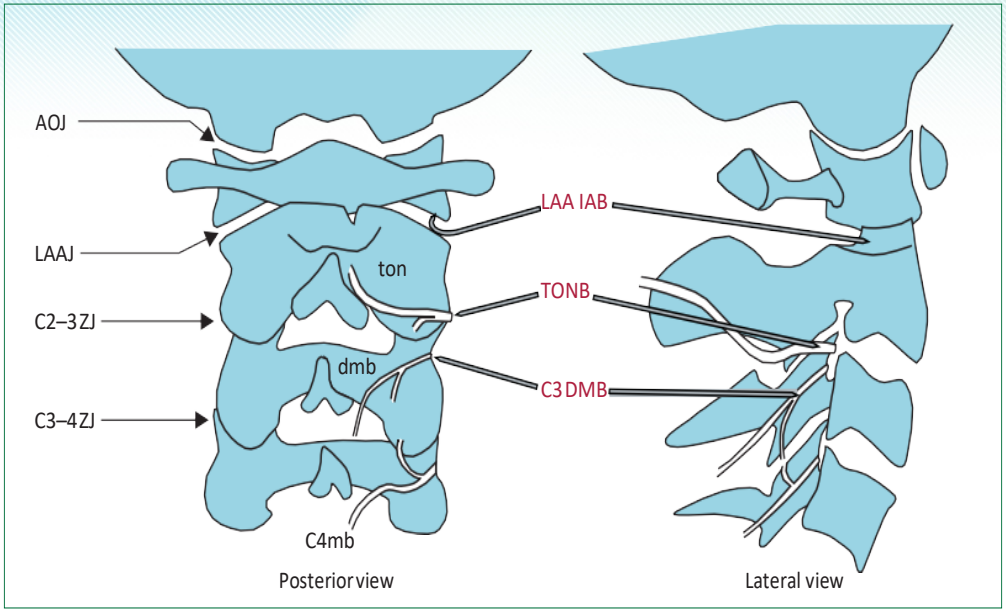
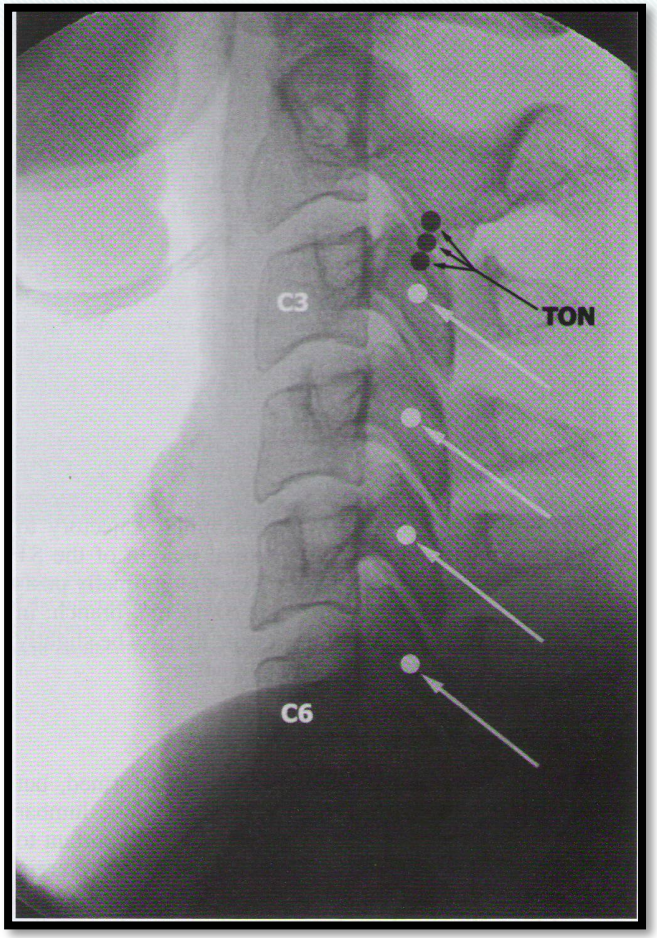


Figure 5: **Posterior and lateral views of the upper cervical spine, showing the leading articular sources of cervicogenic headache, the related nerves, and where needles are placed for diagnostic blocks of these structures**

Red labels and needles point to target sites for diagnostic blocks. AOJ=atlanto-occipital joint. C3 DMB=C3 deep medial branch block. C4mb=medial branch of the C4 dorsal ramus. dmb=deep medial branch of the C3 dorsal ramus. LAA IAB=intra-articular block of the lateral atlanto-axial joint. LAAJ=lateral atlanto-axial joint. ton=third occipital nerve. TONB=third occipital nerve block. ZJ=zygapophysial joint.



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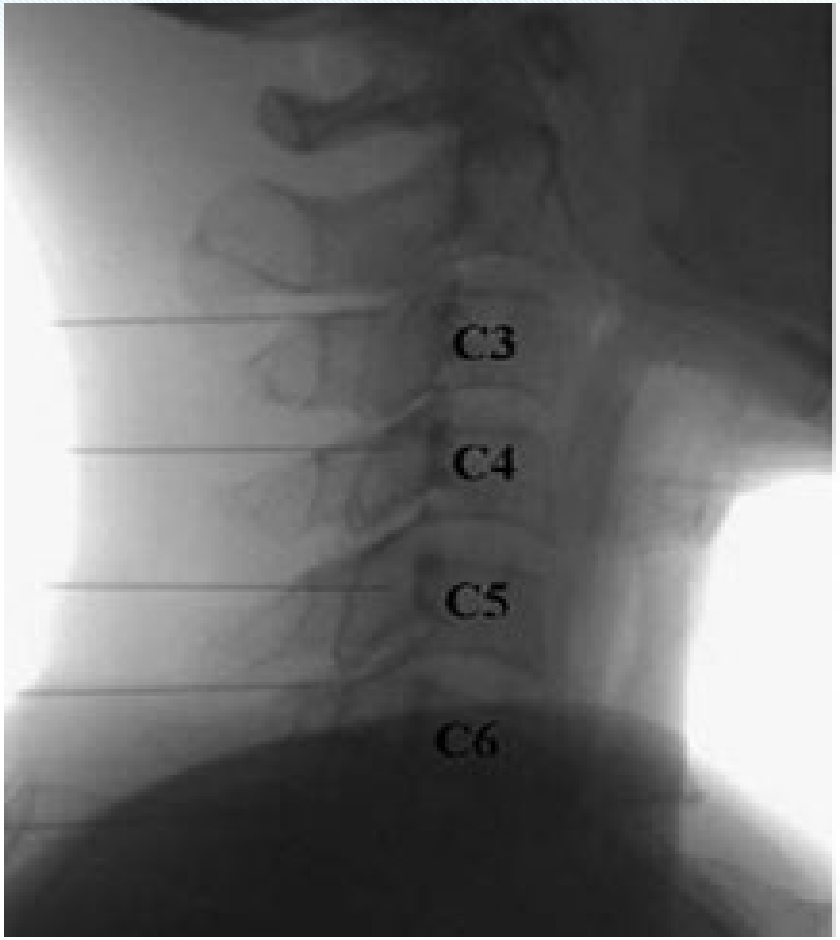

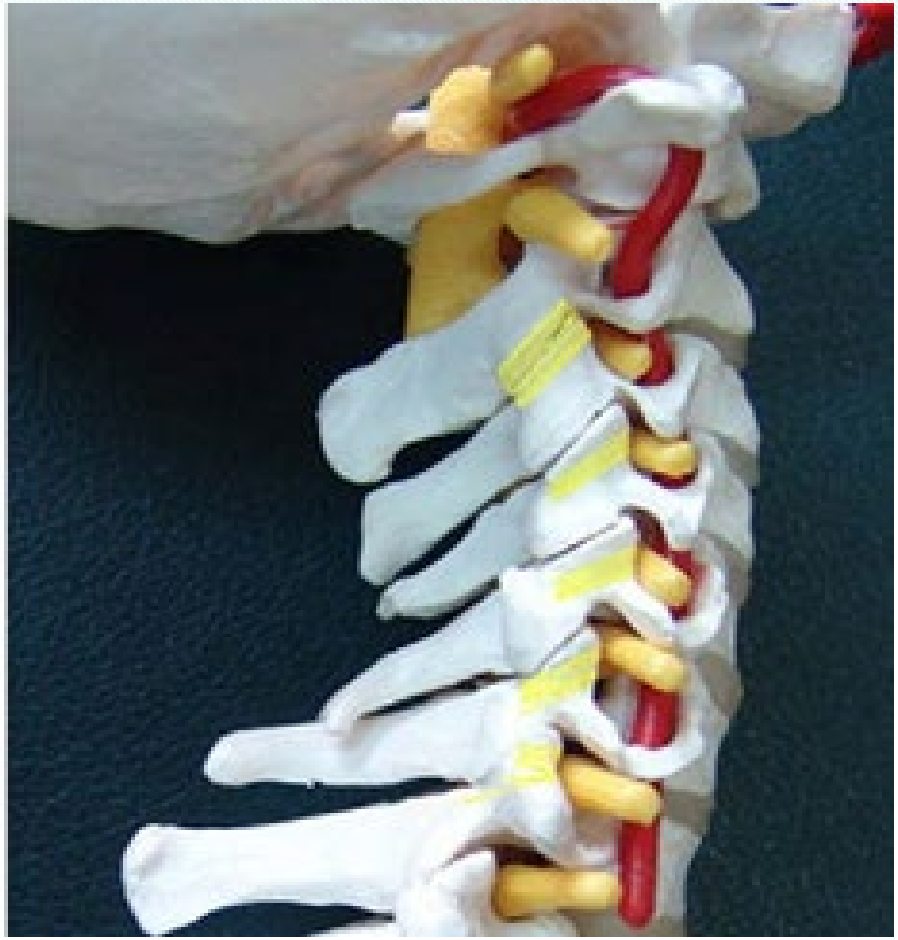

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Chiropractic Spinal and Appendicular Joint Manipulation	•For relief of musculoskeletal pain and to improve range of motion. This technique entails passive movements of the joints.
Mechanical Traction	•A very effective non-surgical procedure that is used to relieve neck, arm, lower back and leg pain. Patients who suffer from degenerated or herniated discs and carpal tunnel syndrome utilize this procedure to help with minimizing pain. The procedure prevents the exertion of pressure on the disc and promotes circulation.
Viceral Osteopathy (CBT)	•For the management of chronic pain in the neck, back, shoulders, and legs. The entire body is examined thoroughly to determine the primary cause of pain. Visceral Osteopathy can be used to treat period pains, asthma, whiplash, painful constipation, among others.
Custom Made Orthotics and Orthopedic Shoes	•Allevio provides custom-made orthotic shoes that will keep your feet comfortable and pain-free. It also helps to keep your feet properly aligned, thus preventing and alleviating pain.
Occupational Health	•We have highly trained occupational therapists who promote health and assist our clients to attain and maintain the highest level of physical, mental and social well-being. We perform active assessments of health risks and educate and train our clients to work safe and efficient in their work environs.

Physical and Vocational rehabilitation

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Cognitive Behavioral Therapy (CBT)	•Allows patients to freely express their thoughts and feelings about their health condition and pain and replaces negative energies and thoughts with positive ones.
Group and Individual Mindfulness Sessions	•Studies have shown that individuals who partake in meditations are more productive, healthier and happier than persons who don't.
Hypnosis	•This form of therapy is used to increase concentration and minimize distractions. Hypnosis is said to be an antidote for reducing pain. It is also used with other forms of pain management therapy to effectively reduce pain.
Psychotherapy	•For the management of chronic pain. It addresses the cognitive, emotional, behavioural, sensory-physiological and interpersonal aspects of pain-related issues and alleviates unnecessary pain thus, reduce suffering.

Psychological Intervention

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Patient information and education for self-management

- How to report pain using the pain scales.
  - Importance of reporting pain as accurately and promptly as possible.
- Use of non-pharmacologic and pharmacologic methods of relieving pain.
- Avoid heavy lifting, trunk twisting, vibrations
- Pain Tool Kit - (paintoolkit.org)
- Importance of notifying staff of unrelieved pain.
- Patients and family members are provided with specific instructions prior to discharge regarding
  - ✓Pain control
  - ✓Pain medications
  - ✓Management of potential side effects

Thank You

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Regenerative Medicine

- The process of replacing or regenerating cells, tissues
- Harness the body's regenerative mechanisms to heal previously irreparable tissues

Regenerative Medicine

- Current estimates indicate that 1 out of 3 patients could benefit from some type of regenerative procedure

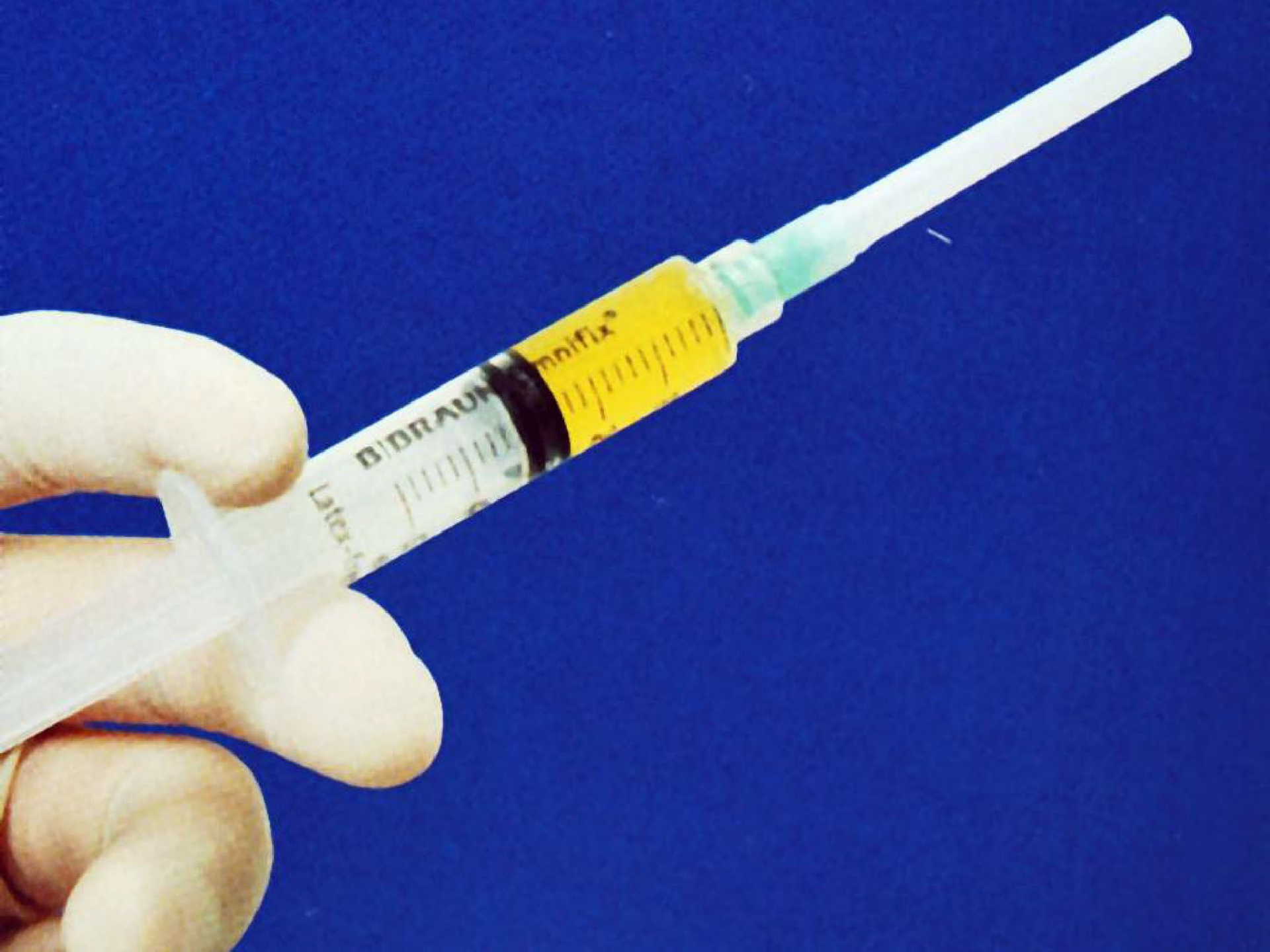
Harris DT, et al. (2007). "The potential of cord blood stem cells for use in regenerative medicine". Expert Opin. Biol. Ther. 7 (9): 1311–1322. doi:10.1517/14712598.7.9.1311. PMID 17727322.

Methods of Regeneration

- Platelet Rich Plasma (PRP)
- Bone Marrow Concentrate (BMAC
- Adipose Tissue - controversial
- Amniotic Tissue/Cord Blood Stem Cells – not in Canada and not proven.

What is PRP?

- *Definition:* A volume of plasma that has a platelet count above that of whole blood
- Platelet count is usually 4-8X that in whole blood
- Platelet rich plasma (PRP) is a biological means to stimulate wound healing and tissue regeneration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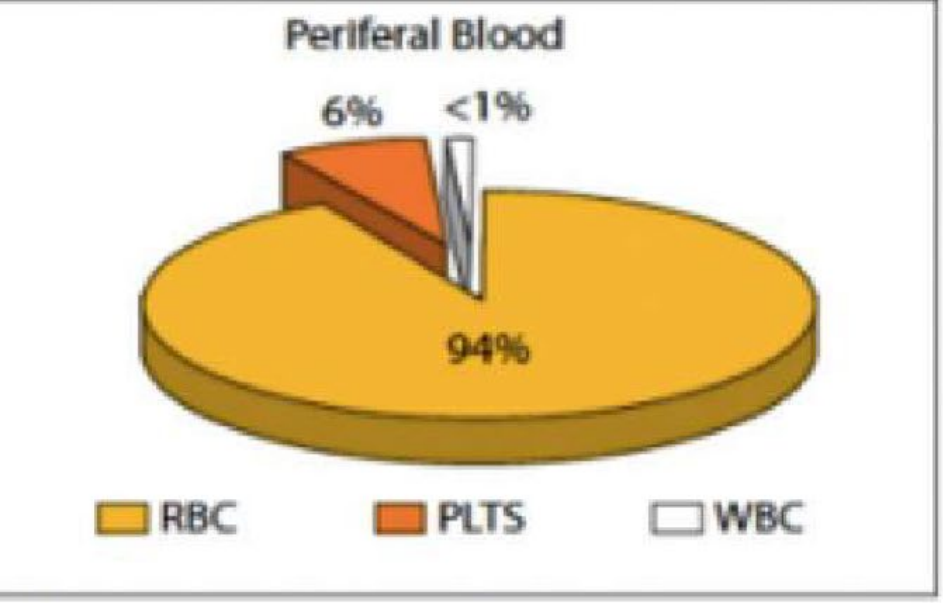
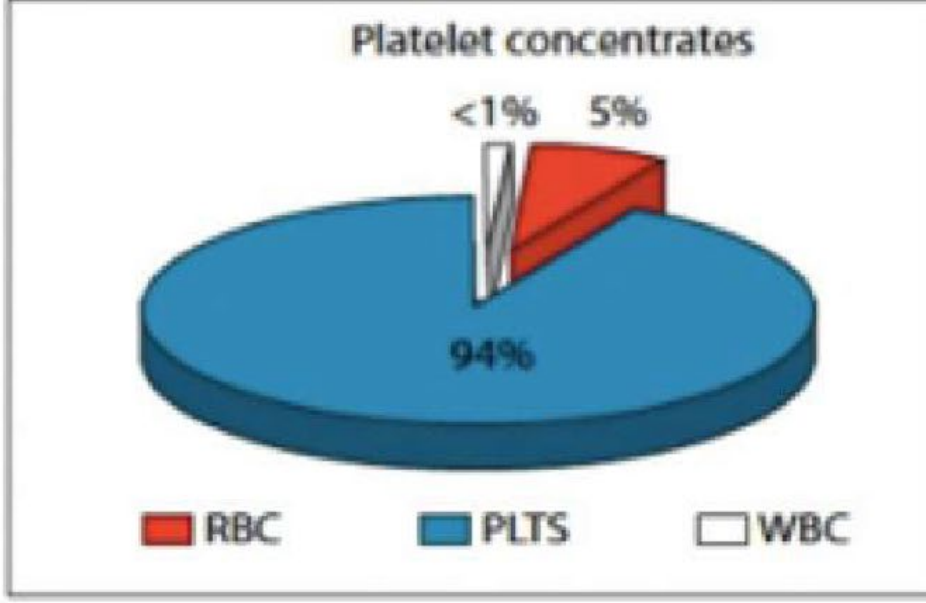
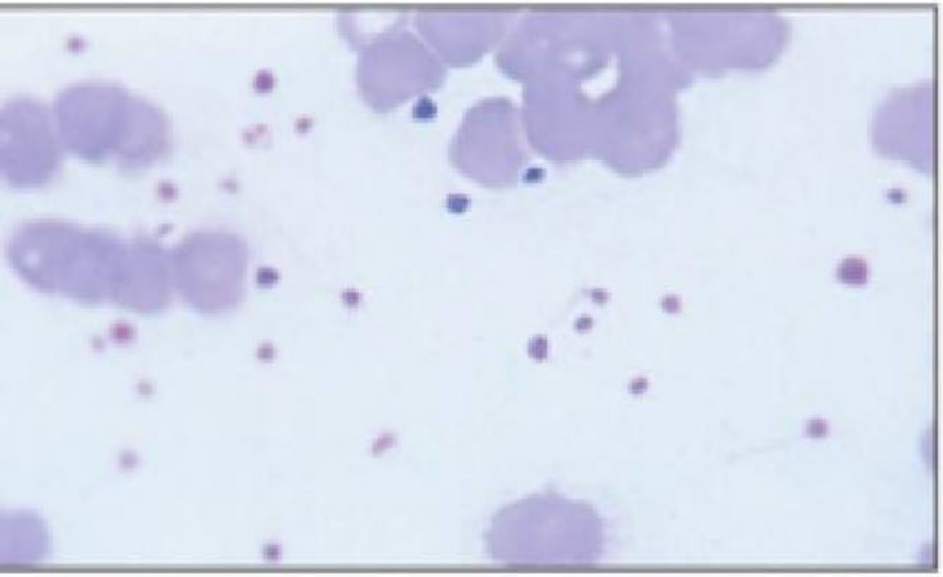


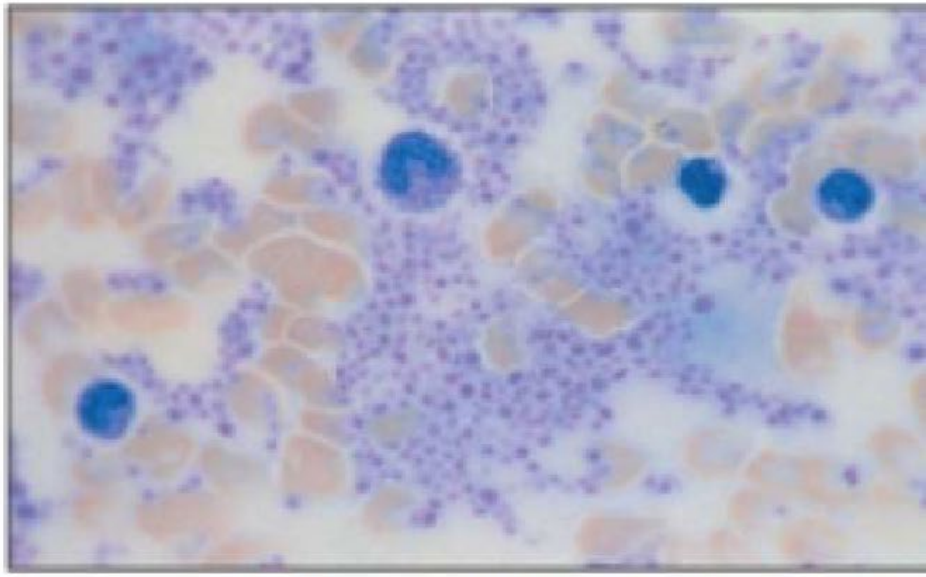
Cell ratios in a normal blood clot.



Cell ratios in platelet rich plasma.



Peripheral blood smear in normal blood



Peripheral blood smear of platelet rich plasma

Why Platelets?

- Platelets contain numerous growth factor proteins stored in alpha granules:
  - Platelet derived growth factor (PDGF)
  - Vascular endothelial growth factor (VEGF)
  - Epidermal growth factor (EGF)
  - Fibroblast growth factor (FGF)
  - Transforming growth factor (TGF)

Platelets

Platelets are activated when exposed to collagen in wall of damaged blood vessel

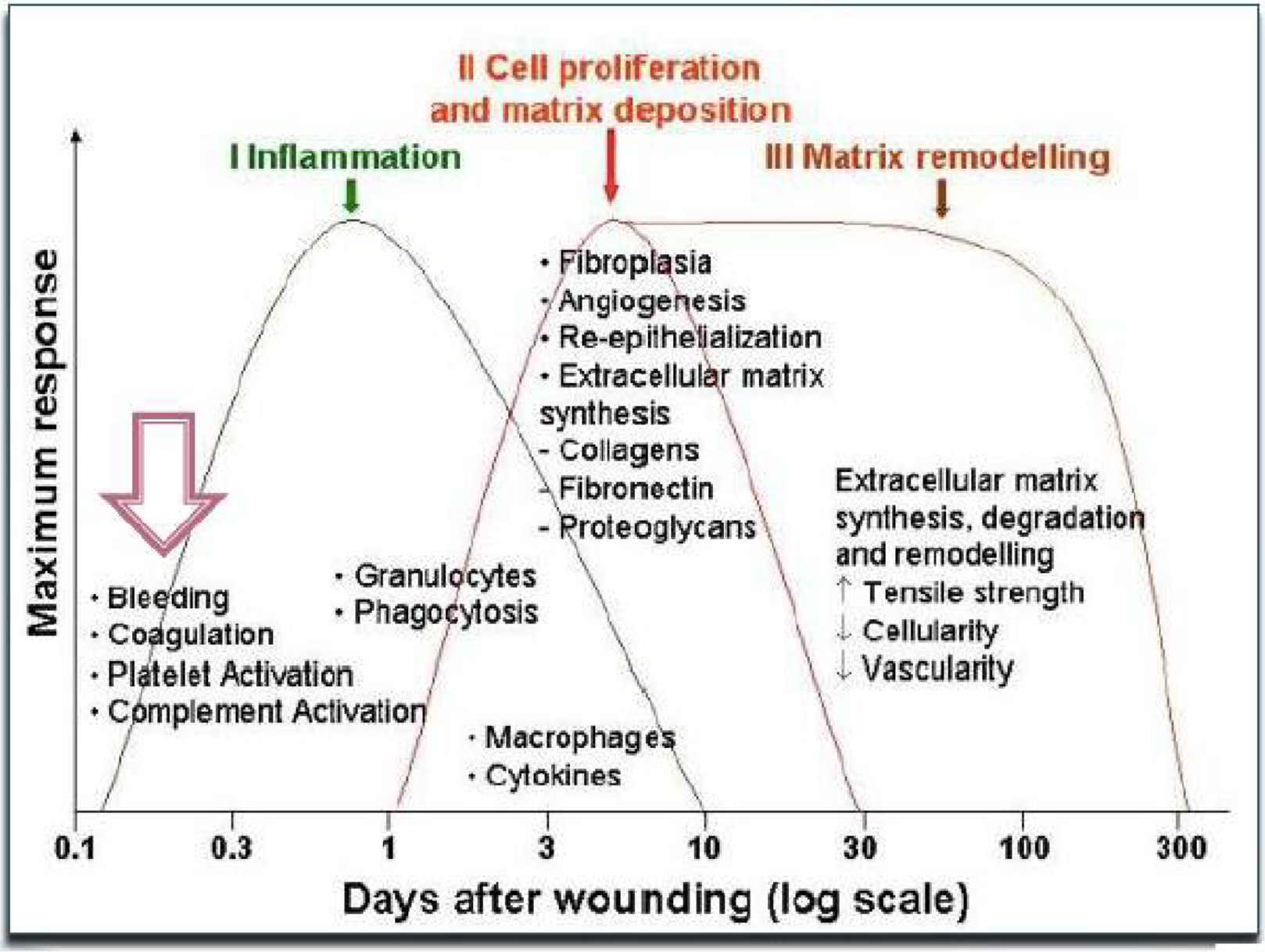
- aggregation to aid formation of clot
- release of more than 30 bioactive proteins that initiate hemostasis and regulate healing

Platelet Derived Growth Factors

Growth factors promote tissue healing by:

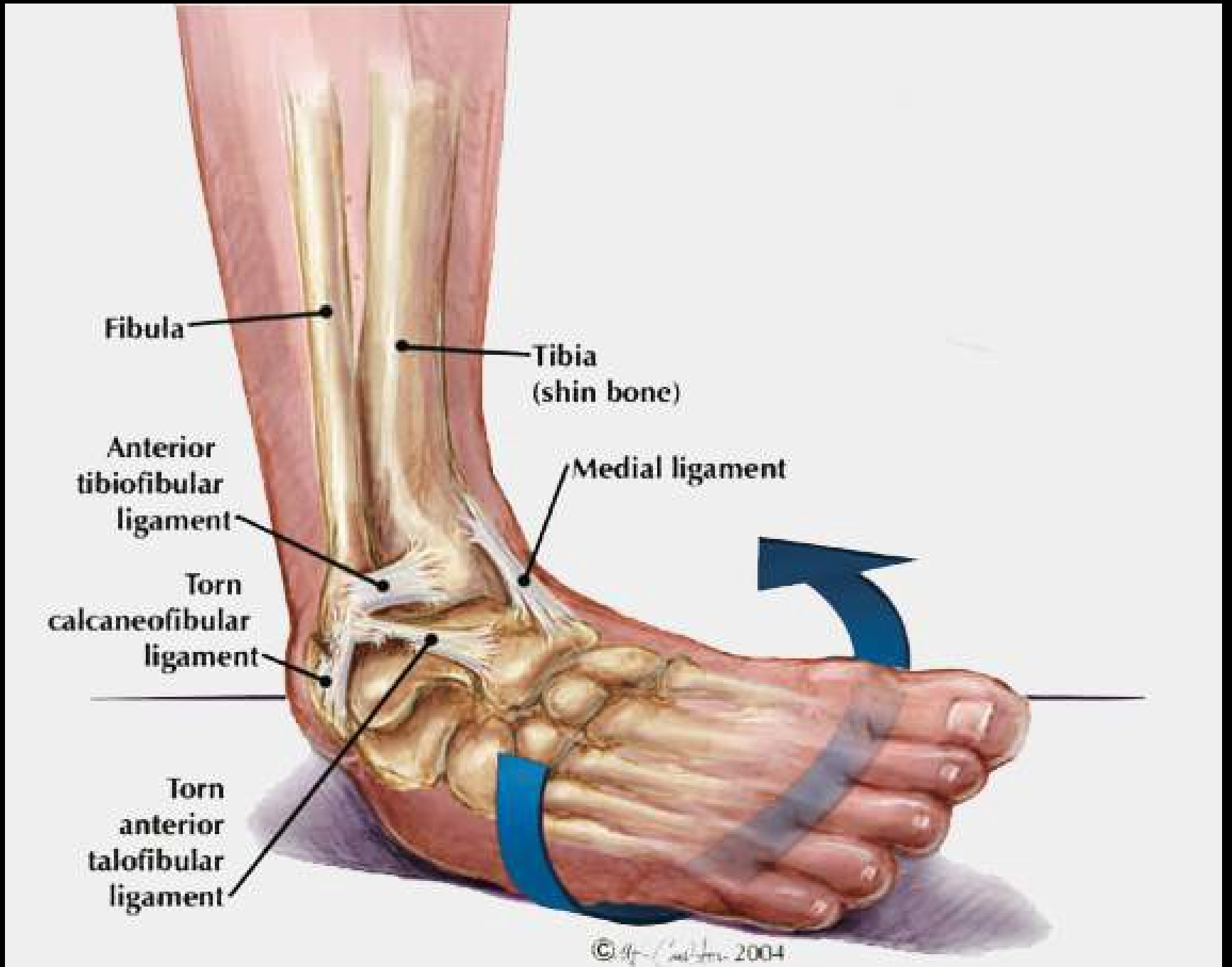
- Stimulates cell replication
- Promotes angiogenesis
- Promotes tissue granulation formation
- Promote growth of extra-cellular matrix

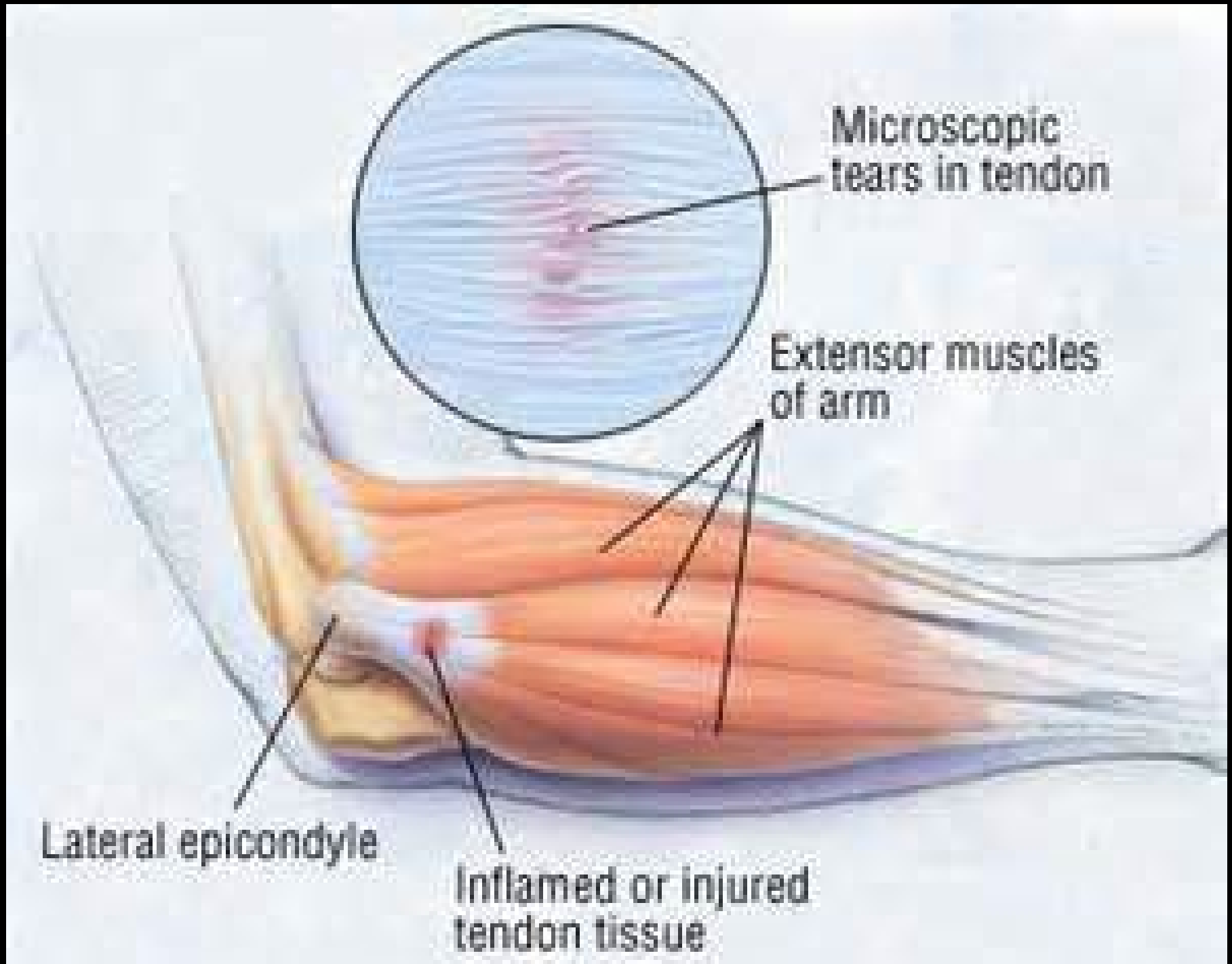
The Wound Healing Cascade

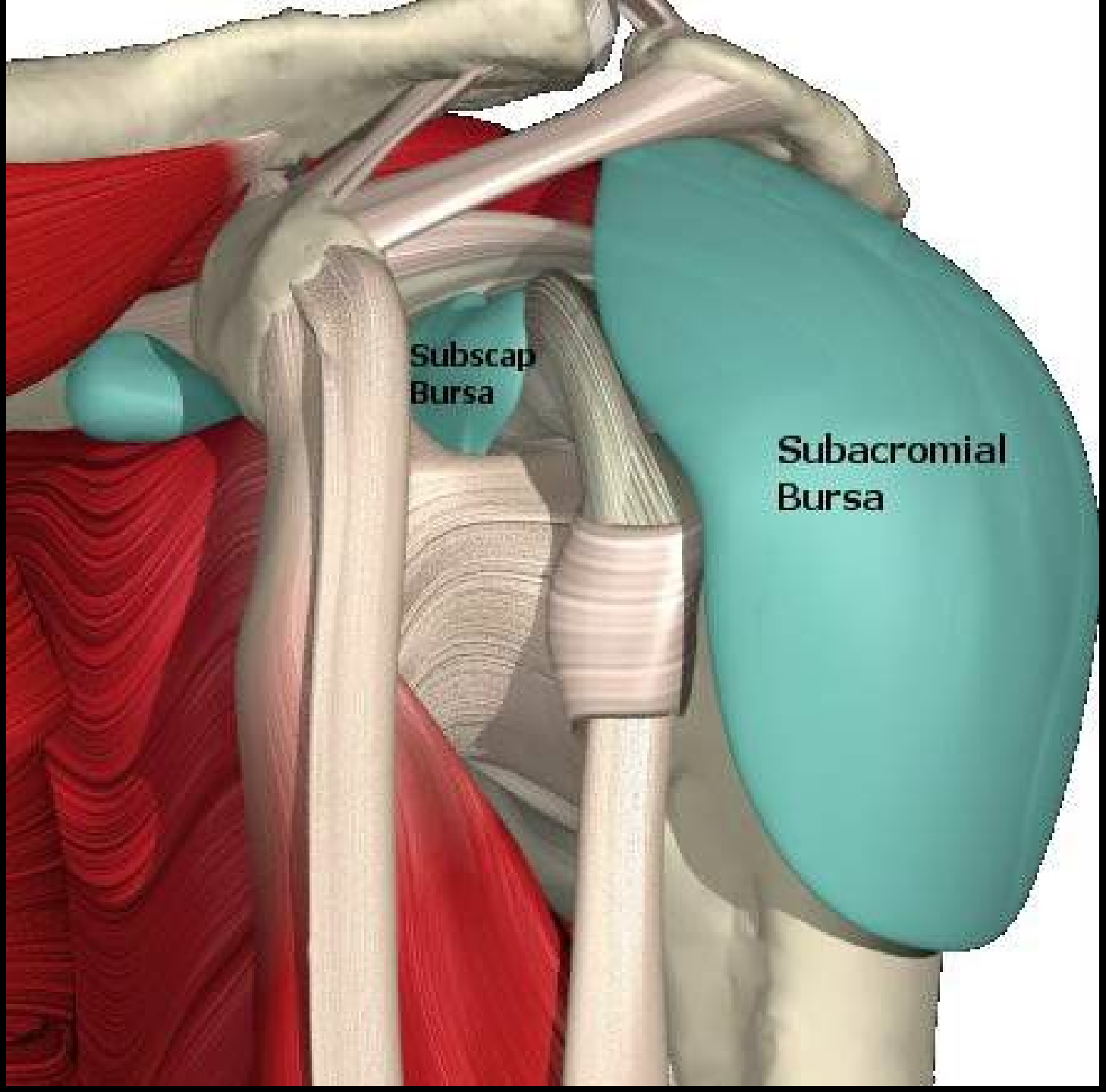


How is it used ?

- Initially, PRP was used by orthopedists and sports medicine physicians to stimulate healing of athletic injuries-tendons, ligaments, muscles and bursa


Fibula
Tibia
(shin bone)
Anterior
tibiofibular
ligament
Medial ligament
Torn
calcaneofibular
ligament
Torn
anterior
talofibular
ligament
© 2004


Microscopic tears in tendon
Extensor muscles of arm
Lateral epicondyle
Inflamed or injured tendon tissue


Subscap
Bursa
Subacromial
Bursa

Later physicians began to study its use for treatment of chronic conditions

Application to chronic MSK and degenerative conditions

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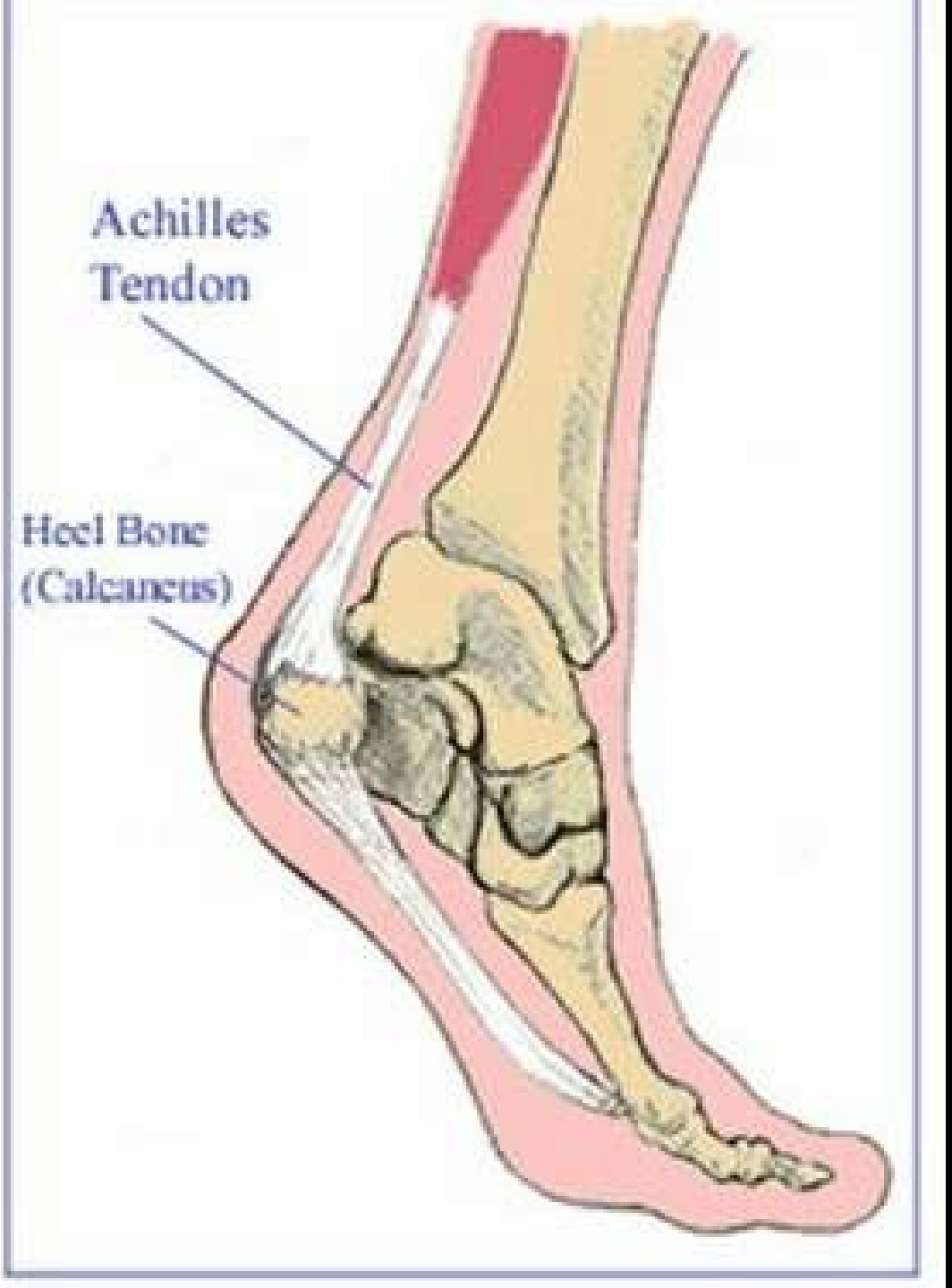
Healthy knee joint

Osteoarthritis

Trochanteric Bursitis Pain Pattern


Bursa
Bone
Tendon
©MMG 2001


Achilles
Tendon
Heel Bone
(Calcaneus)

New applications are being developed to treat spinal disorders

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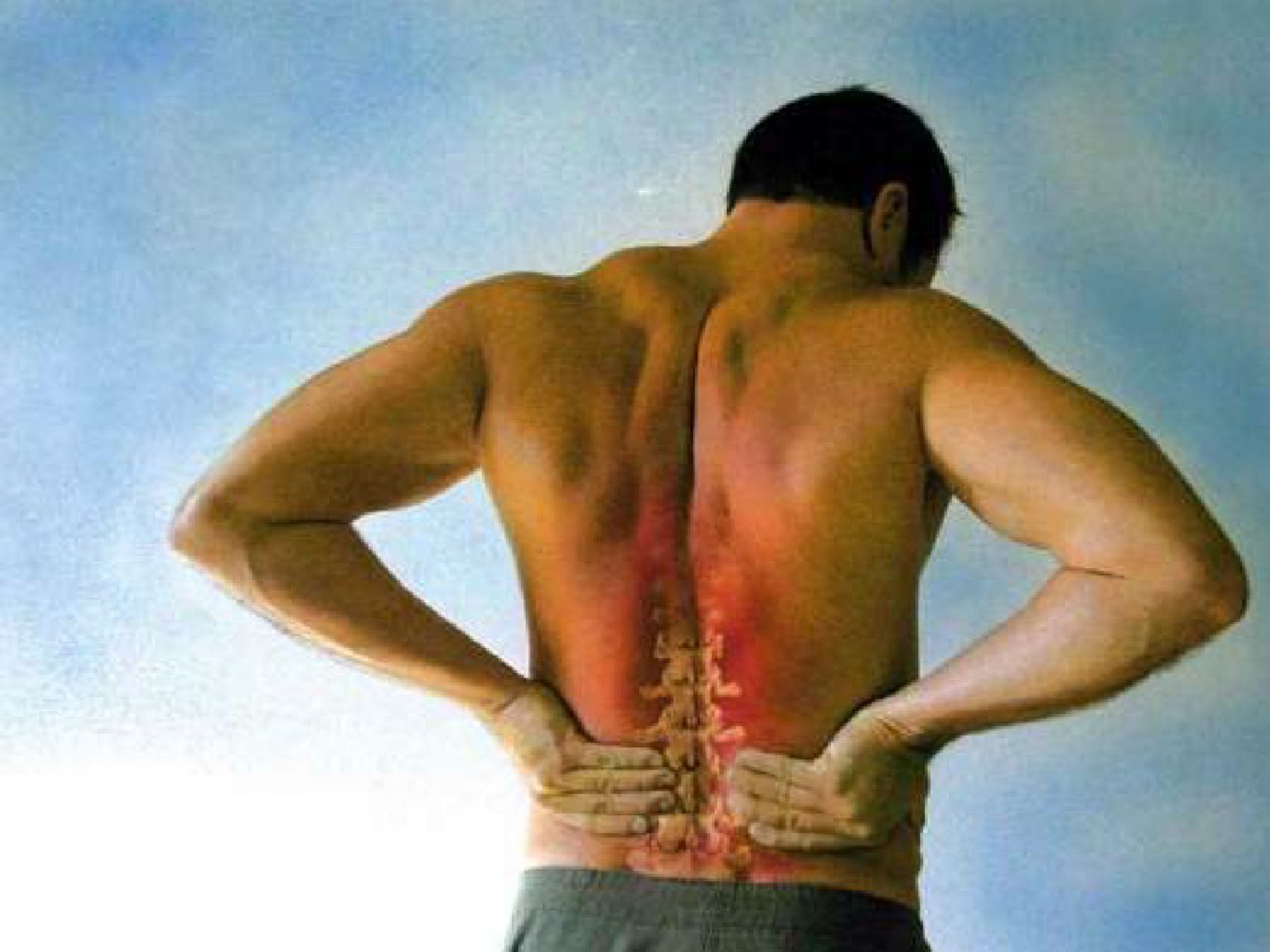

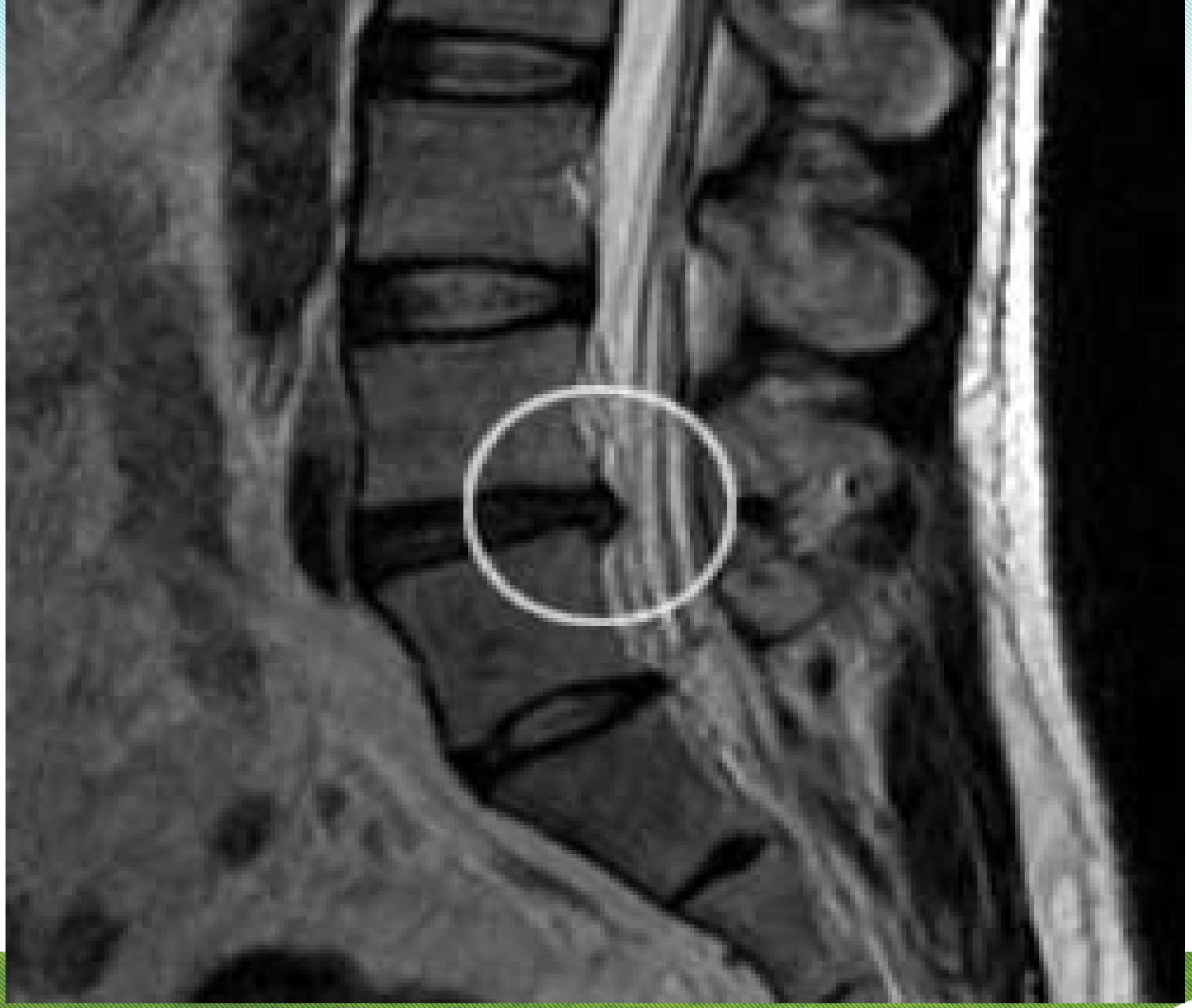

Disc Herniation with radiculopathy

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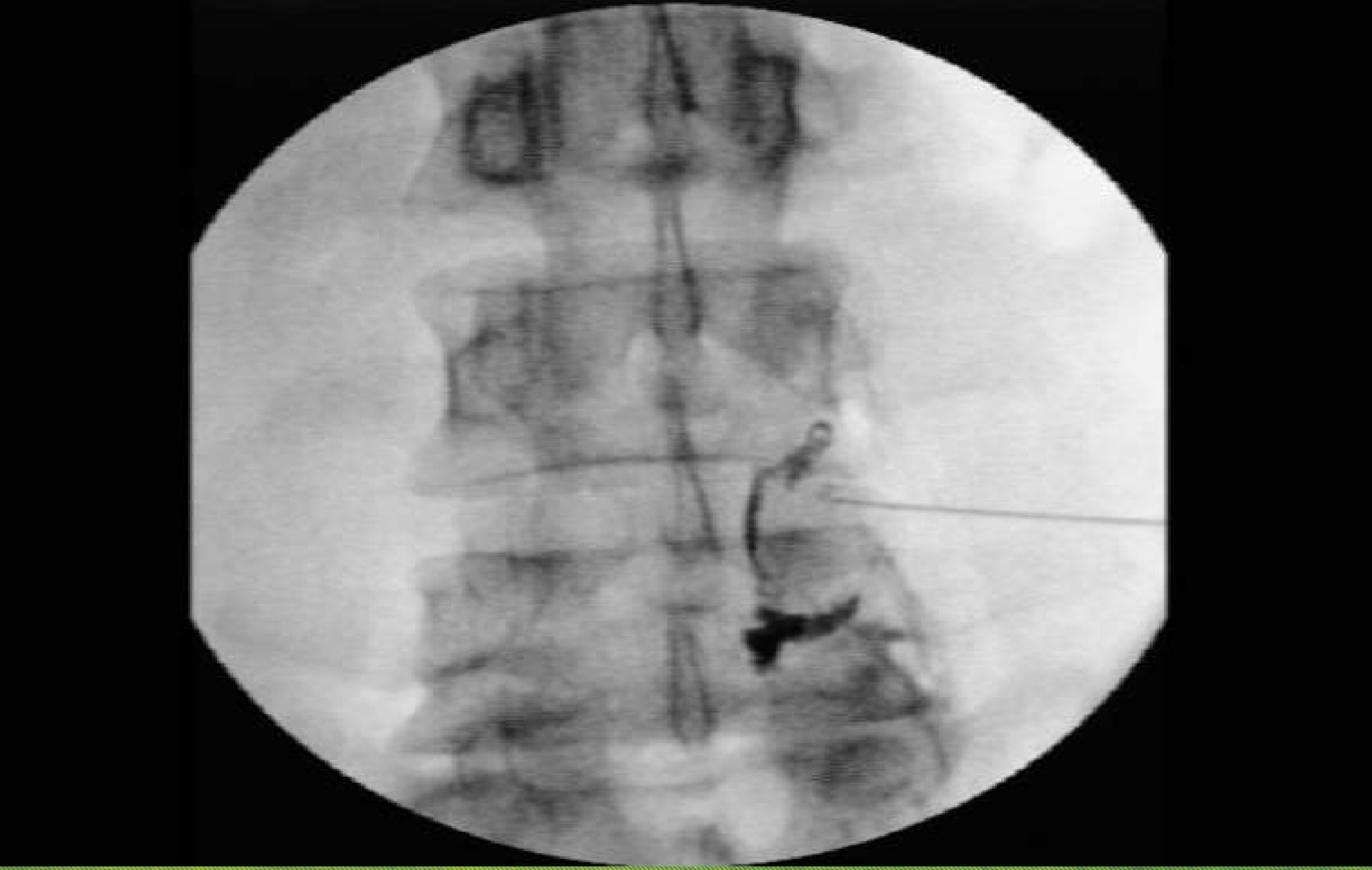

Transforaminal epidural injecting PRP

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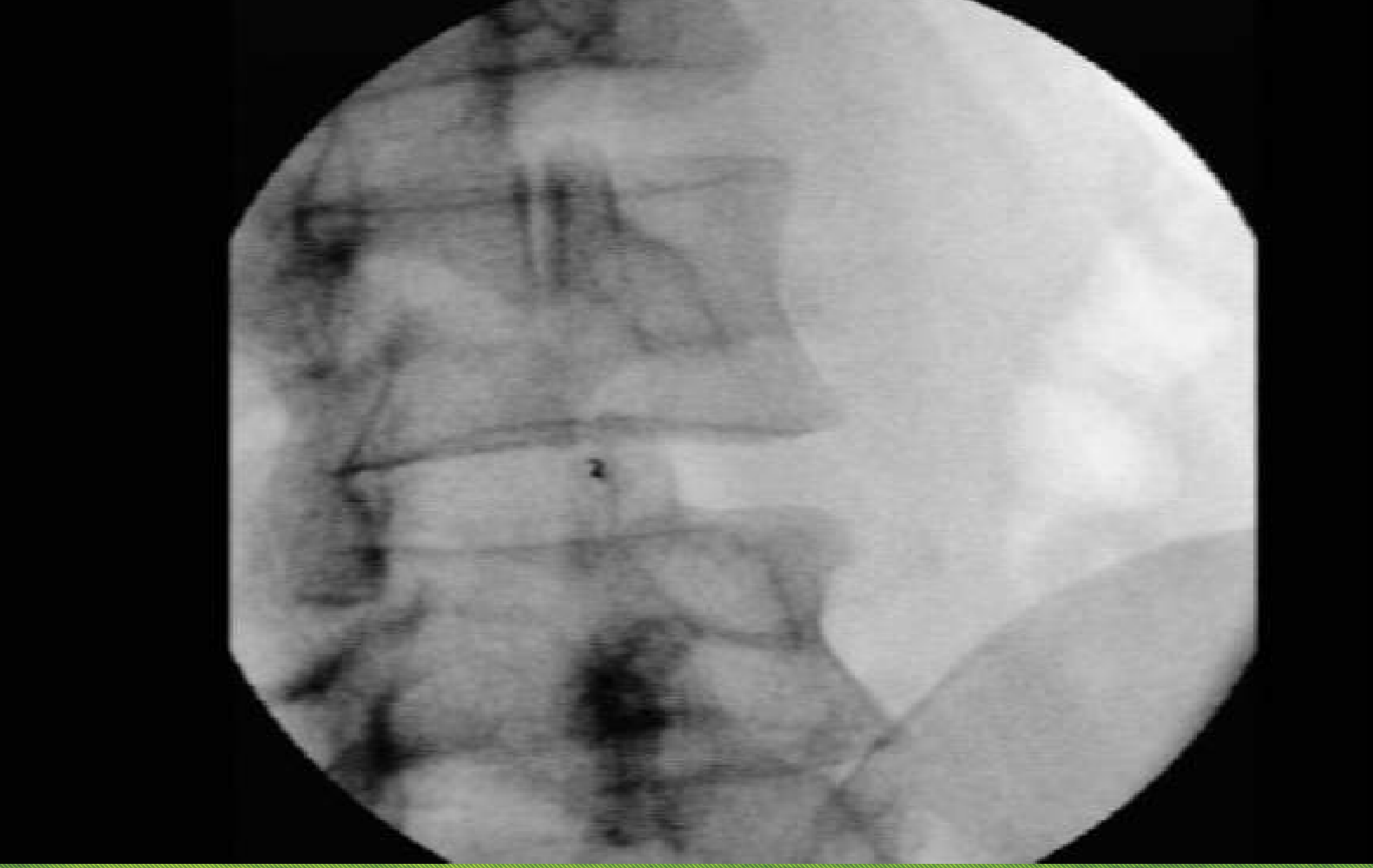

Intra-articular facet injection with contrast and PRP

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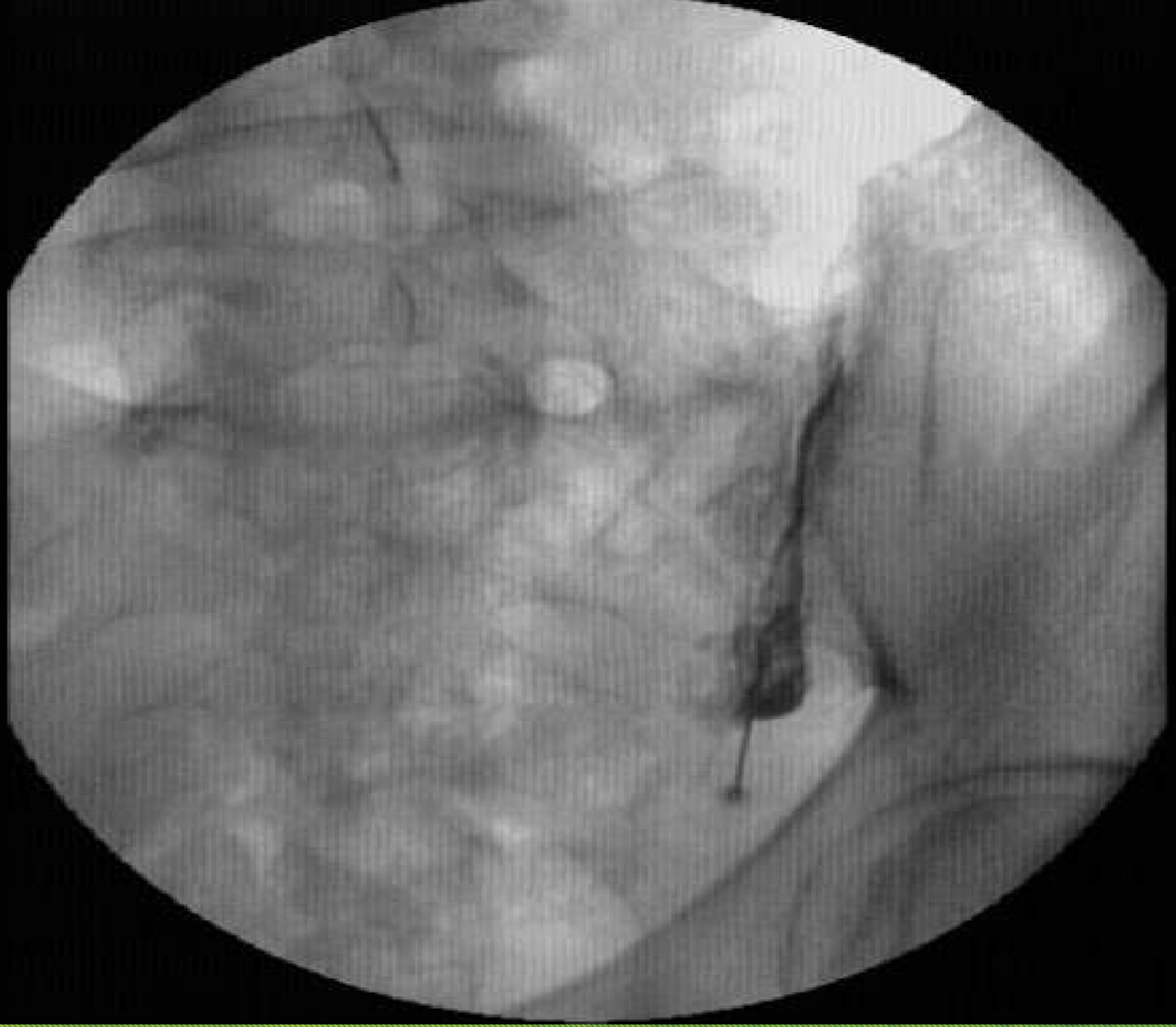

Right Intra-articular injection with contrast of Sacroiliac joint

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Pain Clinic Uses:

- PRP injections are used to treat patients who have had temporary relief from steroid injections and require repeat injections are a regular basis-

- Patients with various tendon, ligament and joint injuries as well as spine pain

Biological Therapy

- Results can take up to 3 months
- Patients are instructed to rest the injured area for 1-6 weeks
- Patients are then started on a program of physical therapy and re-evaluated after 12 weeks

Harvesting

- This is processed in a centrifuge in order to separate and concentrate platelets


Platelet-poor plasma
Buffy coat (platelets and white blood cells)
Red blood cells

All injections are image guided with US or Fluoroscopic

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Results-Intra articular PRP

Laboratory results agree with recent RCT's

Level of Evidence	Author	Diagnosis	PRP Formulation	Outcome
RCT	***Dragoo AJSM 2014***	***Patellar Tendinopathy***	***Leukocyte rich***	*VAS scores improved at 12 weeks but not at 26 weeks*
RCT	***Krogh AJSM 2013***	***Elbow Tendinopathy***	***Leukocyte rich, RBC poor***	*No difference at 3 mo vs steroid or saline*
RCT	***Peerbooms AJSM 2010***	***Elbow Epicondylitis***	***Leukocyte rich***	***significant difference vs steroid***
RCT	***Raeissadat PRT 2014***	***Elbow Epicondylitis***	***Leukocyte rich***	*No significant difference Vs Whole Blood*
RCT	***Thanasas AJSM 2011***	***Elbow Epicondylitis***	***Leukocyte rich***	***significant difference vs whole blood***

What do I need to know?

Pre injection protocol

- NSAID's have a negative effect on platelet function as they may decrease GF release
  - Most authors recommend stopping for 5 days before and up to two weeks after injection

Am. J. Phys. Med. Rehabil. & Vol. 93, No. 11 (Suppl), November 2014

What do I need to know

Duration of effect

- Varies depending on severity of disease
- For knee OA, treatment effect begins to decline 6-9 months post treatment with further loss of benefit at 24 months

General Indications

- Tendon/ligament pathology
- Bursitis
- Osteoarthritis of major joints
- Annular tear of lumbar disc

Possible Future Uses

- Facet joint arthritis
- SI joint syndrome
- Radicular pain
- Spinal stenosis

Contraindications

- Anti-platelet medications-ASA, Plavix, Ticlid
- Anti-coagulants-Coumadin
- Bleeding/clotting disorders
- Thrombocytopenia < 50K
- Blood borne cancers-lymphoma, leukemia

Contraindications

- Other blood borne diseases (malaria, rocky mountain spotted fever)
- Current fever with systemic infection or infection at the site of injection
- Patient who have multiple medical issues whose health is unstable

Am. J. Phys. Med. Rehabil. & Vol. 93, No. 11 (Suppl), November 2014

Risks of procedure

- Risks associated with needle puncture into tissue
- Local infection secondary to unsterile needle placement or PRP preparation
- Pain at injection site

Risks

- Note that, because the product is derived from the patients own blood, there are no risks usually associated with blood products like transfusion reaction, allergic or immune reaction

- Unlike pharmaceutical products, there are no risks associated with injection of the substance

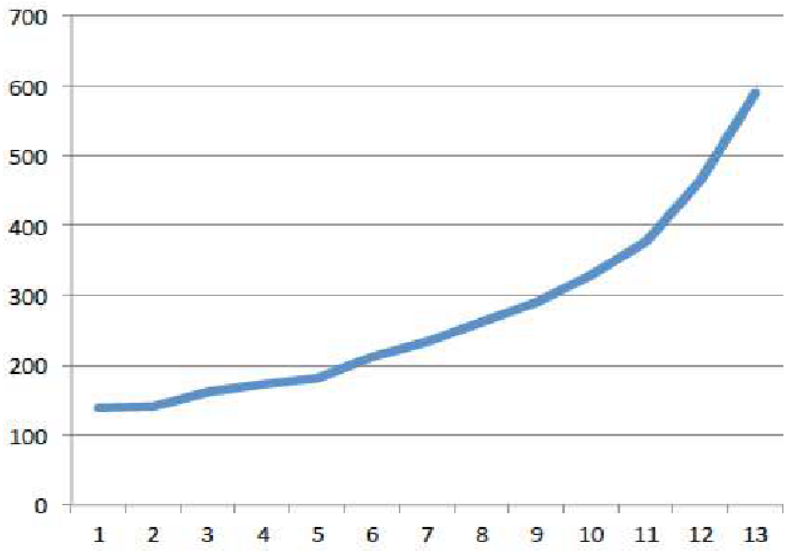
History of Platelet-Rich Plasma

Dramatic Rise in PRP References in the last decade

Over 7000 total references

573 new PubMed references in 2013 alone

PubMed Platelet Rich Plasma References per Year 2000-2013



Studies

Indication	Level 1 Studies	Level 2 Studies
Elbow Epicondylitis	x	
Patellar Tendon	x	
Plantar Facitis	x	
Rotator Cuff Tear	x	

Indication	Level 1	Level 2
Annular Tear of Lumbar Disc	x	
Osteoarthritis of Knee	x	
Trochanteric Bursitis of Hip		x

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Lumbar Intradiscal Platelet Rich Plasma (PRP) Injections: A Prospective, Double-Blind Randomized Controlled Study

Yetsa Tuakli Wosornu, MD [1]; Alon Terry, MD [1]; Elizabeth E LaSalle, BS [1]; Caitlin K Gribbin, BA [1]; Kwadwo Boachie-Adjei, BS, CPH [1]; Joseph T Nguyen, MPH [1]; Jennifer L Solomon, MD [1]; Gregory E Lutz, MD [1]

[1] Physiatry Department, Hospital for Special Surgery - New York, NY

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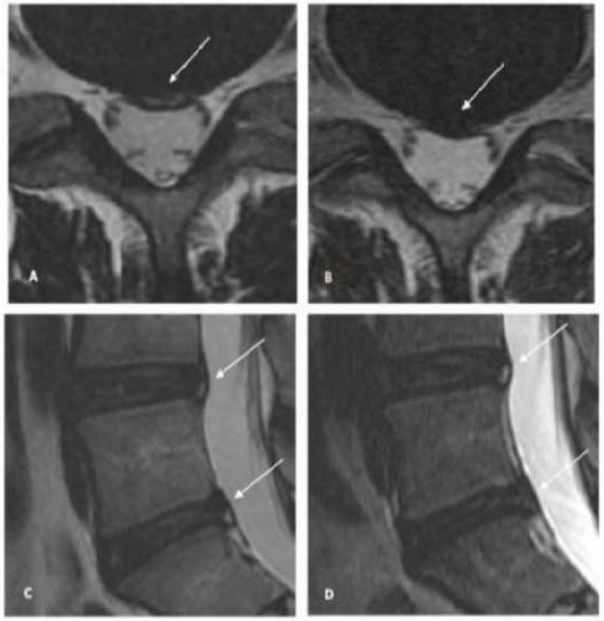
Purpose

- Determine if a single intradiscal PRP injection at time of discography has therapeutic value compared to control (contrast) injection



MRI imaging of study subject prior to study participation in 2011 (left) and post study participation in 2013 (right) (a) L5-S1 T2 axial image of individual in 2011 (b) L5-S1 T2 axial image of individual in 2013 with resolution of the HIZ (c) T2 Sagittal image 1 of individual in 2011 (d) T2 Sagittal image of individual in 2013 with 2 resolution of the HIZ at L5-S1. Of note is that the HIZ at L4-5 is the same or larger 3 despite also being treated with PRP.

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Inclusion

- LBP>6 months
- Failed conservative treatment
- Maintained disc height of > 50%
- Size of protrusion < 5 mm

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Methods

- Patients underwent discography to identify presence of concordant pain and annular disruption
  - Randomized (2:1) to receive either 1-2 ml of PRP (treatment group) or 1-2 ml of additional contrast agent (control group)

- Follow-up data collected at 1 wk., 4 wks., 8 wks., 6 mo., and 1 yr. by an independent observer

- Patients in control group offered PRP treatment at 8 wks.

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Conclusion

- 58% (14/25)of patients who received intradiscal PRP demonstrated improvements in pain, function, and satisfaction in compared to 13% (2/15) of control
  - No complications or adverse effects

- Intradiscal PRP is a potential cell therapy for a specific subset of patients with discogenic low back pain

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What about facet disease?

- In a two year, 24 patient study conducted by Marco Palmieri MD at NYU Stony Brook, they found that pain and function improved at 1 month and 3 months but returned to baseline by 6 and 12 months

PAIN Practice

Explore this journal >

Original Article

Steroid vs. Platelet-Rich Plasma in Ultrasound-Guided Sacroiliac Joint Injection for Chronic Low Back Pain

Varun Singla MD ✉, Yatindra K. Batra MD, Neerja Bharti DNB, Vijay G. Goni MS, Neelam Marwaha MD

First published: November 2016 Full publication history

Abstract

Background

Despite widespread use of steroids to treat sacroiliac joint (SIJ) pain, their duration of pain reduction is short. Platelet-rich plasma (PRP) can potentially enhance tissue healing and may have a longer-lasting effect on pain.

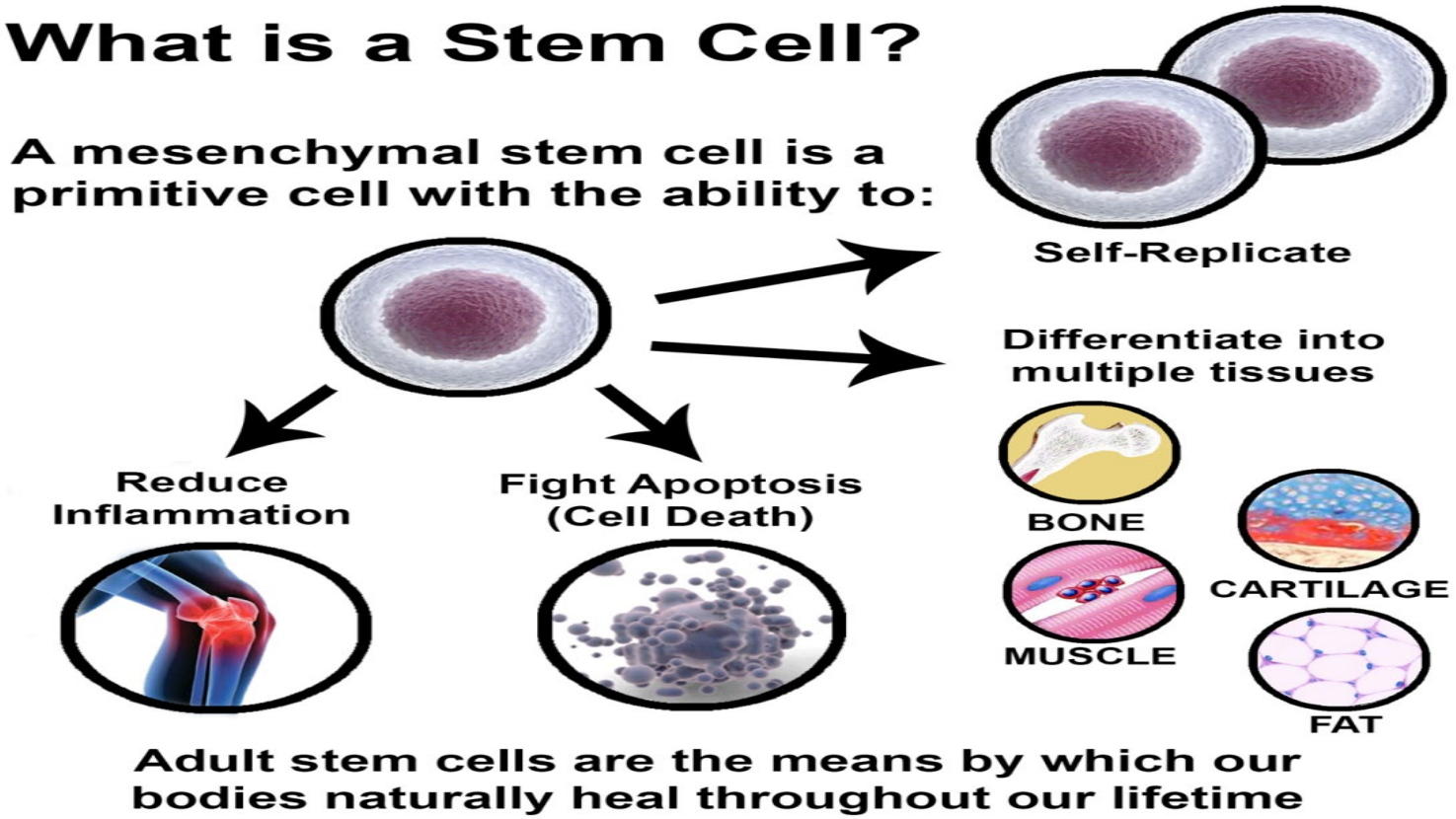
Objectives

To assess the efficacy and safety of PRP compared with methylprednisolone in ultrasound-guided SIJ injection for low back pain.

Study Design

Prospective randomized open blinded end point (PROBE) study.

Mesenchymal Stem Cells -MSCs?



Stem Cell Therapy

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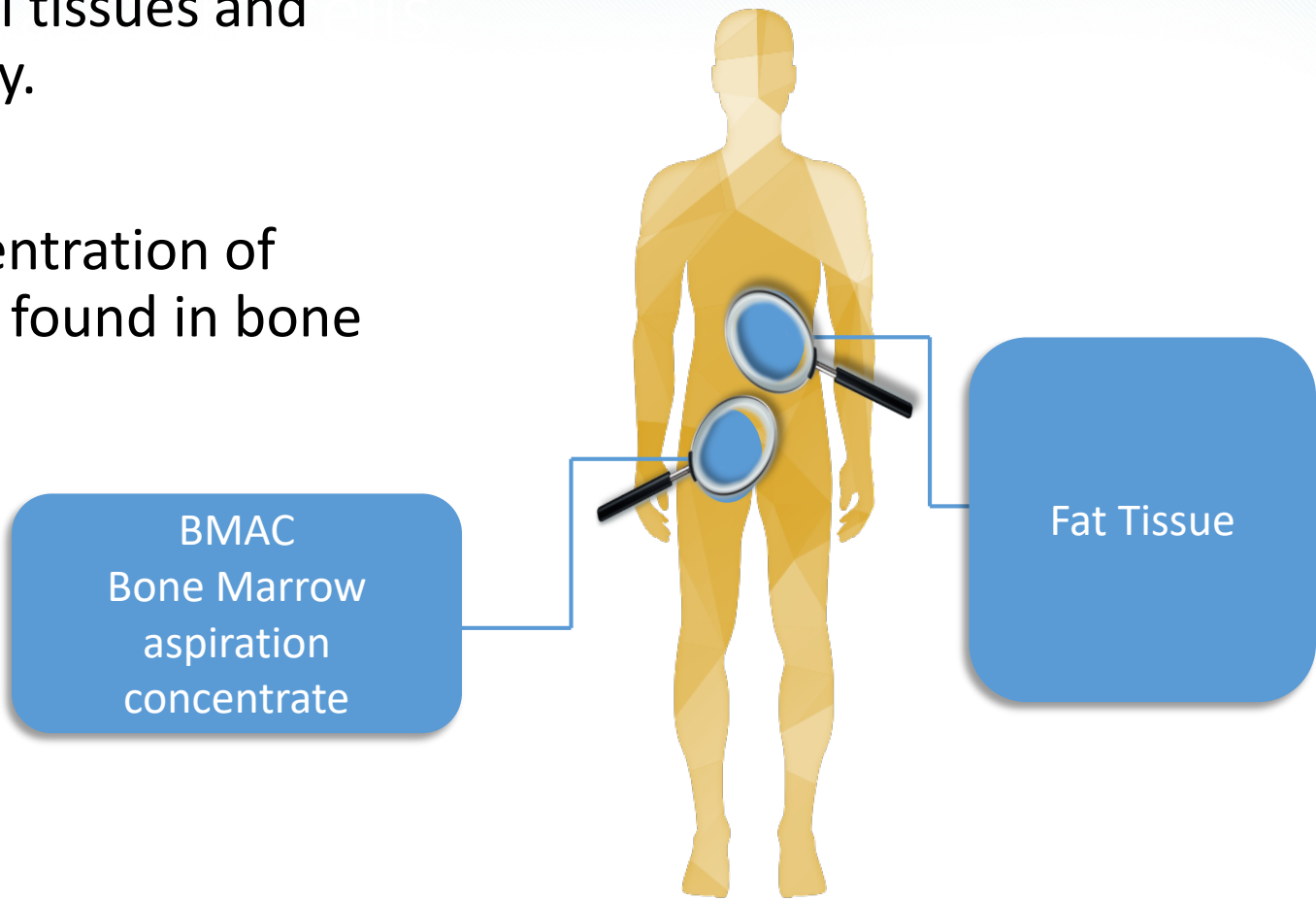
- Mesenchymal (Adult) stem cells can be found in all tissues and organs of the body.

- The highest concentration of these cells can be found in bone marrow and fat.



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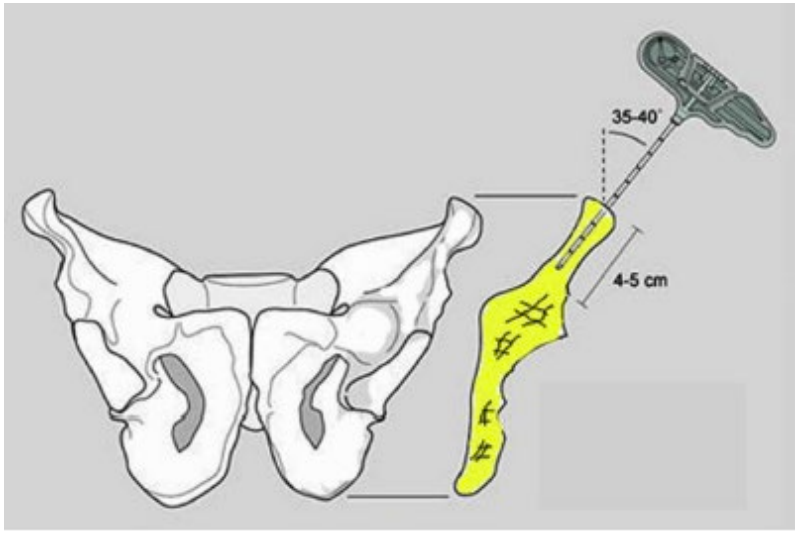
- Diamond tip BMA needle preferred
- Under X-Ray guidance and squaring of the iliac crest, guide in plane from lateral to medial to the illium
- Use firm pressure to allow tip to enter bone
- Use of excessive axial forces unnecessary
- Stop to test for marrow aspiration if no loss of resistance
- Use manual technique when entering bone marrow cavity after loss of resistance
- Avoid Local Anesthetics – toxic to chrondrocytes
- Ropivacaine reported to be the least toxic LA



BMA Technique

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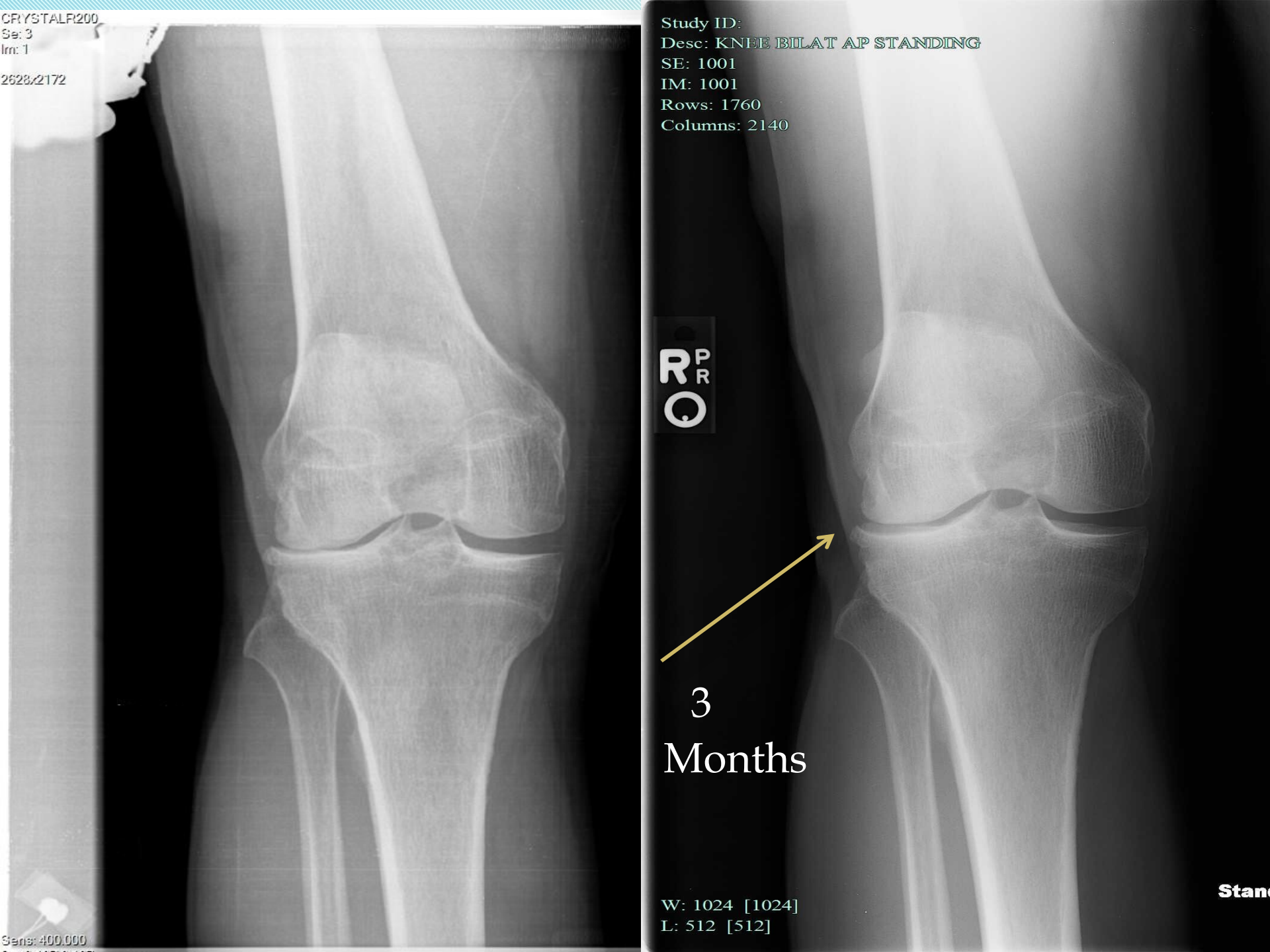
ORTHOPEDIC SUCCESS

- Patients reported 3-4 years pain free
- Avoid morbidity and mortality associated with total joint replacement
- Knees may improve in 2 months
- Shoulders can take up to 3 months to improve
- CMC joint can be better overnight
- Backs tend to improve in week or more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Desc: KNEE BILAT AP STANDING
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W: 1024 [1024]
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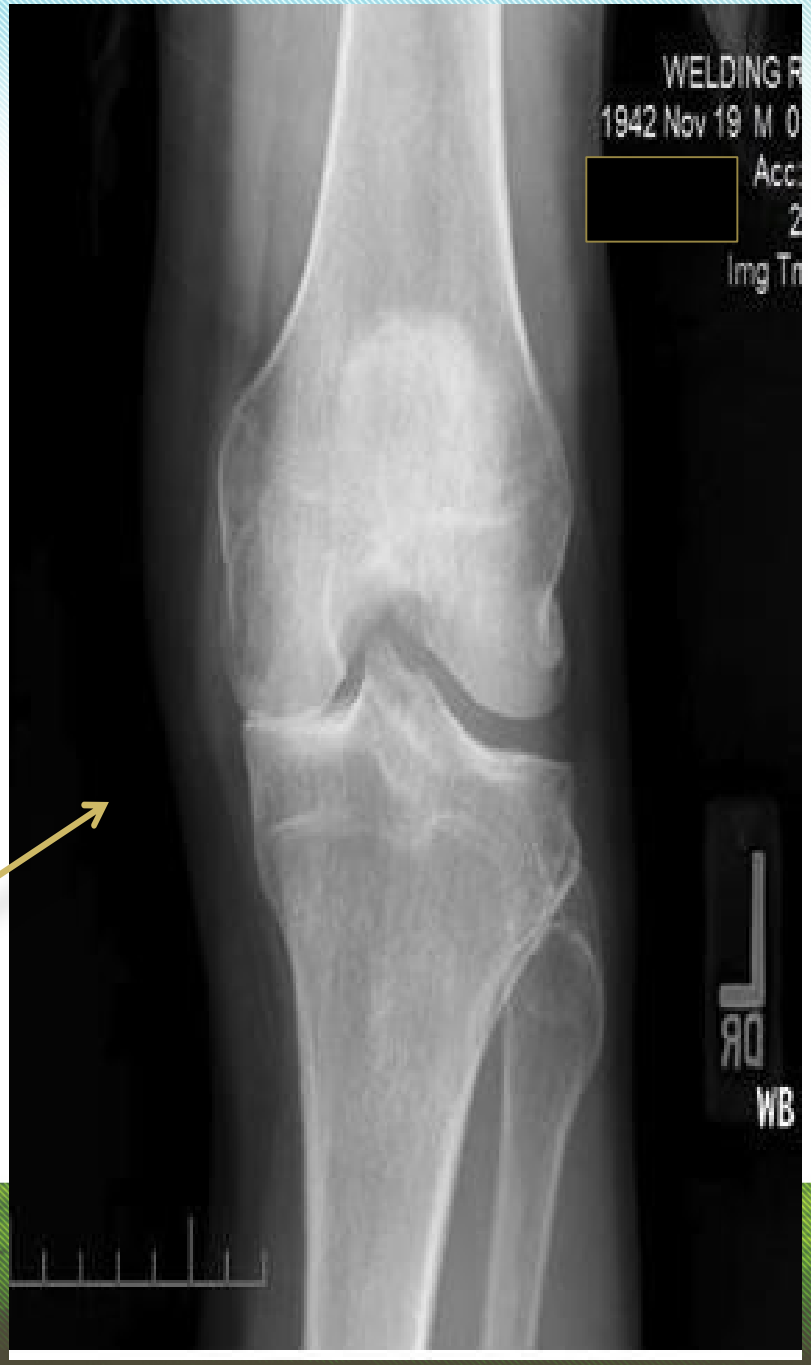
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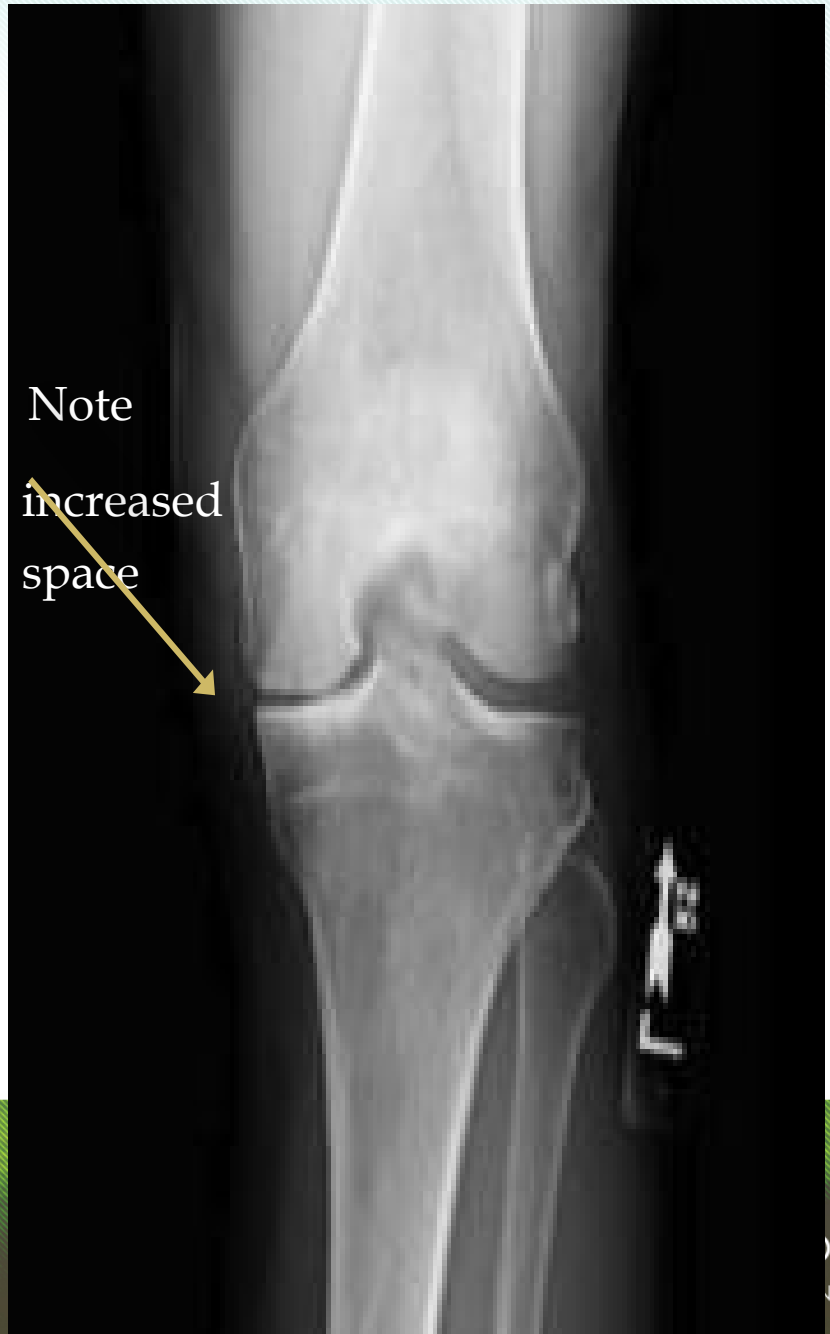
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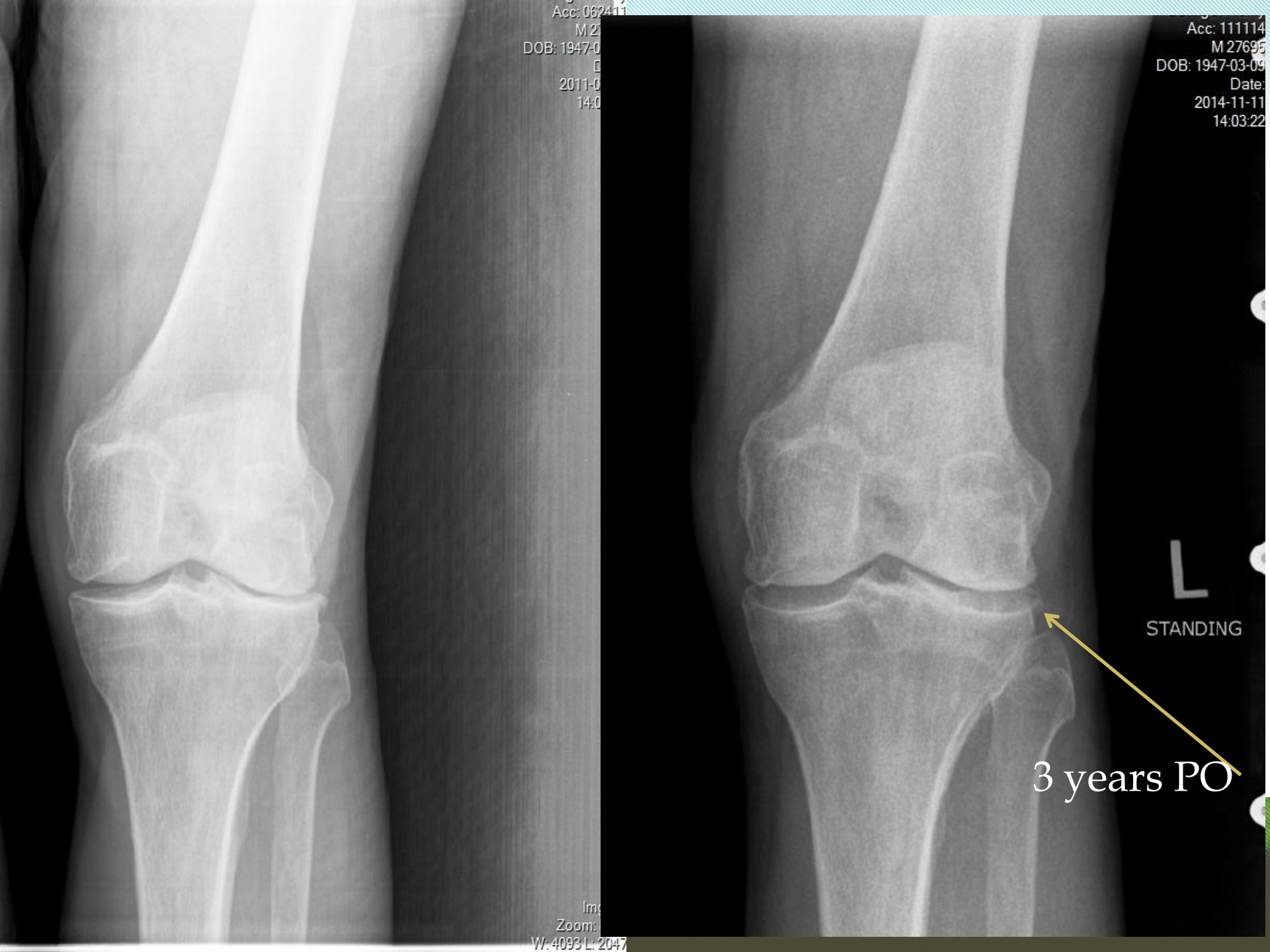
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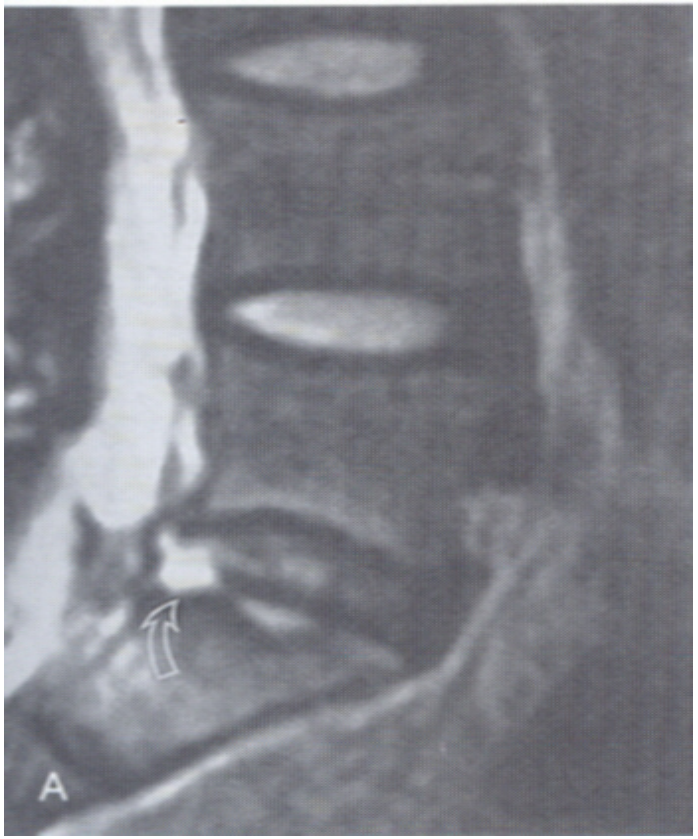
Structural Source of CLBP

- Intervertebral Disc reported 39-43% prevalence
  - Non healing Annular tears
  - 30-55 year olds
- Facet Joint reported 32%
  - Older patients - 60 year olds
- SI joint reported 18 %

Internal Disc Derangement

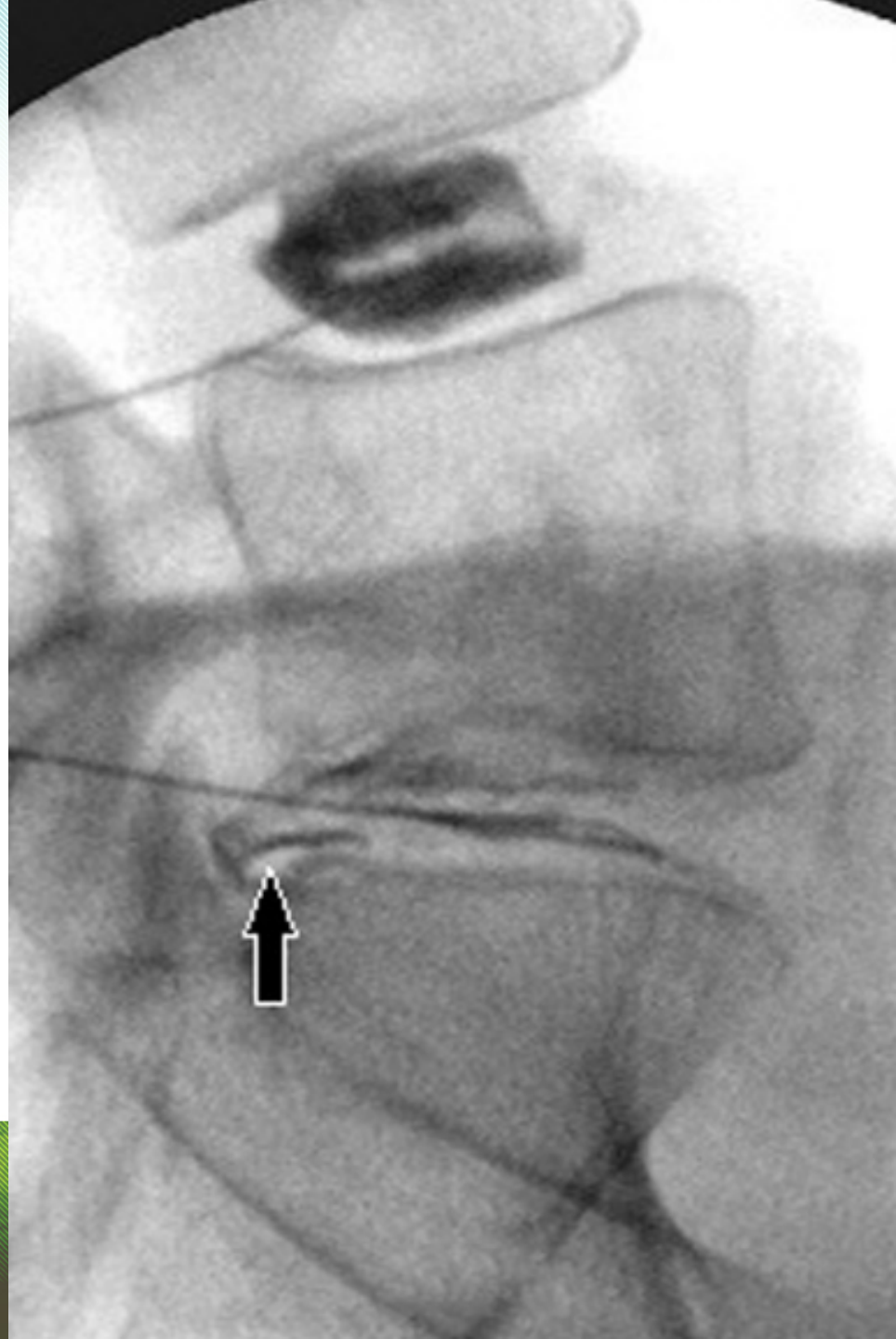
HIZ onT2 MRI of L5-S1 disc



Discogenic CLBP & IDD >> DDD

- IDD
  - Injury /Non healing painful Annular fissure >>>>>>
    - Inflammatory reaction
    - Macrophage/Mast cell invasion
    - Cytokine (IL1-6, TNF-a, PG-2)
    - Growth factor
- *These changes culminate in altered mechanics and impaired chrodrocyte function: >>>>>> leading to DDD*
    - Reduced nutrition & metabolic byproduct removal
    - Altered biophysical context
    - Cell loss
    - Changes in matrix turnover
    - Altered biomechanics

Structural repair of the annular fissure may be more successful if disk degeneration is arrested and/or reversed



- Physical Therapy (& other conservative options)
- Spinal Fusion
- Artificial disk replacement,
- Intradiskal heating,
- Intradiskal neurolytic
- Reparative OR Regenerative concept?
  - ✓*Treat pain*
  - ✓*Slow down or reduce onset of degenerative cascade?*

Effective treatment for painful disks is an unmet clinical need

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Conclusion

- Early/precise **diagnosis** with reasonable work up
- Use the **least invasive** procedure to achieve most functional result - **Get to the source of pain**
- Keep them **moving** - specific therapeutic & general!
- **Combine** rehabilitation plan with pain interventions
- Regenerate, heal rather than mask the pain!
- Lets not Overpromise!
- Avoid prescribing **disability, dependence, disuse, depression!!**
- Avoid emergence of **chronic pain syndrome"**
- *" It is not always what you do but who you do it on"*

Thank You

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MEDICINAL CANNABIS FOR CHRONIC PAIN

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Learning Objectives

- Endocannabinoid System
- Phytocannabinoids
- History of Medicinal Cannabis
- Brief look at the Legislative landscape
- Current Evidence

TERMINOLOGY

- **Cannabinoids:** A class of compounds that act on cannabinoid receptors in the human body

- **Endocannabinoids:** Cannabinoids that are naturally produced in the body (endogenous)

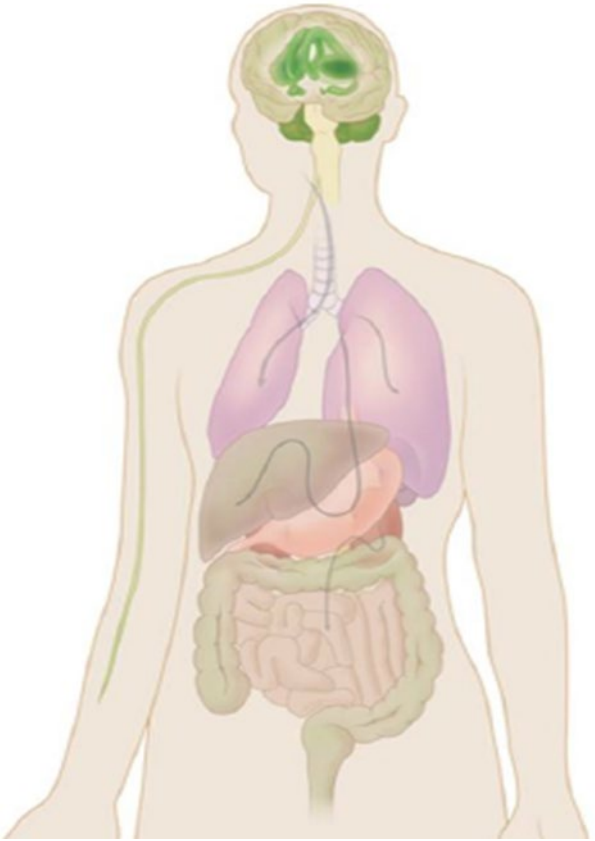
- **Synthetic Cannabinoids:** Laboratory-synthesized compounds that bind to cannabinoid receptors, e.g. pharmaceuticals (i.e. Nabilone)

Endocannabinoid System

This system is complex and is responsible for extensive physiological and pathophysiological activity.

Inflammation
Appetite
Metabolism
Cardiovascular function
Bone density
Synaptic plasticity
Pain

Memory
Sleep
Reward/addiction
Stress regulation
Mood
Reproduction
Digestion



CB1 present:

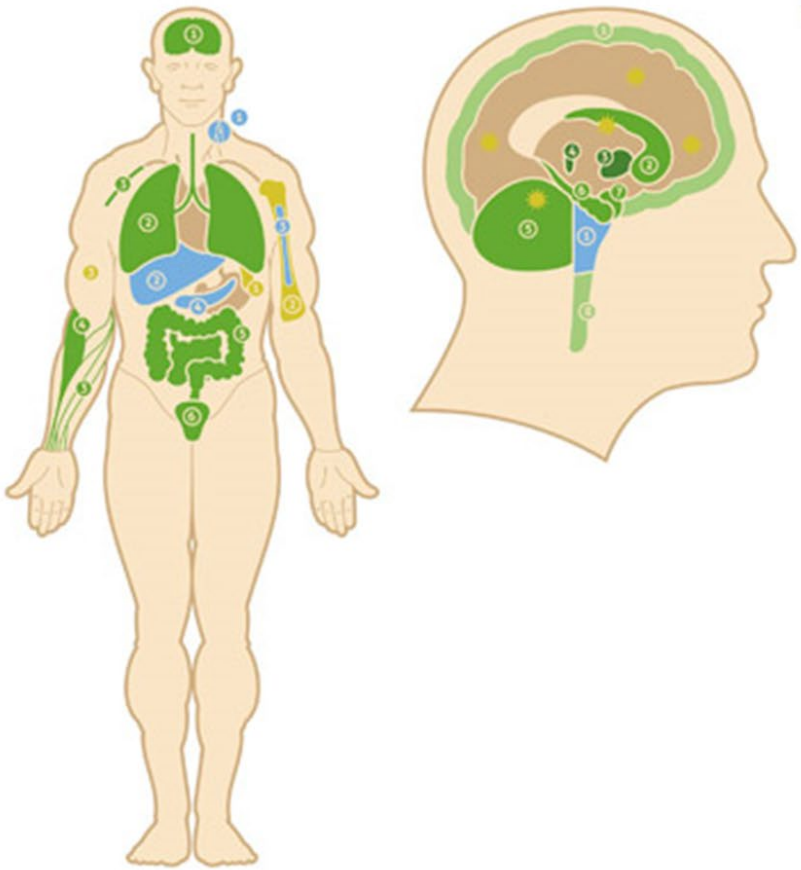
1. brain
2. lungs
3. vascular system
4. muscles
5. gastrointestinal tract
6. reproductive organs

CB2 present

1. spleen
2. bones
3. skin

CB1+CB2 present

1. immune system
2. liver
3. bone marrow
4. pancreas



CB1 present:

1. cortex
2. caudate nucleus and putamen (nucleus acumbens)
3. basal ganglia
4. hypothalamus
5. cerebelum
6. hippocampus
7. amygdala
8. spinal cord

CB2 present

glial cells

CB1+CB2 present

1. brainstem

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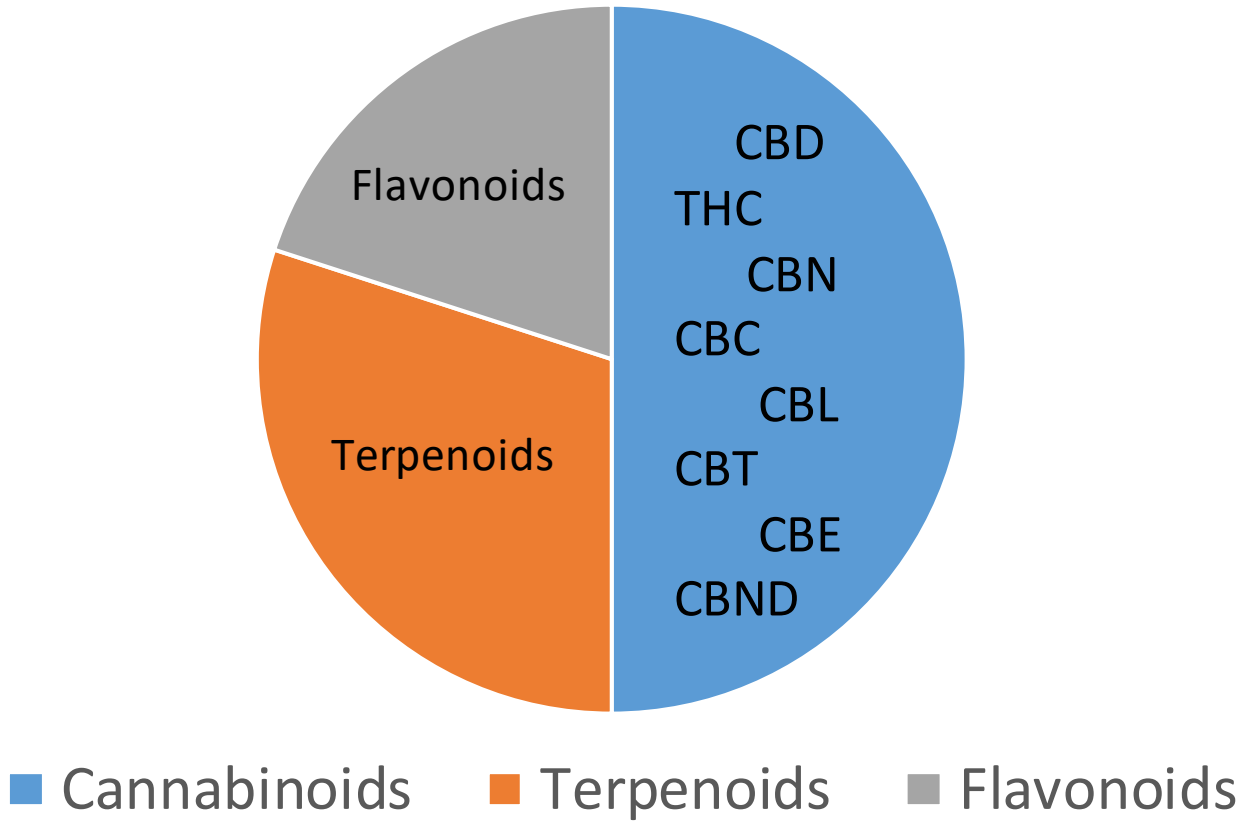
- CB1 activation Inhibits release of:

I. Glutamate
II. Serotonin
III. Dopamine
IV. Acetylcholine
V. Noradrenaline
VI. Cholecystokinin
VII. D-aspartate

Chemistry and Composition (there are 400 chemicals in cannabis and over 60 are referenced as cannabinoids).



Cannabis Aromas and much more

- Flavonoids and Terpeniods:

anti-oxidant
anti-anxiety
anti-inflammatory antibacterial
anti-neoplastic (prevent tumor)
anti-malarial

- Effects on female population of long term THC exposure reduces LH, FSH, Prolactin and GH
- May increase cardiac events with patients with pre-existing heart disease
- Review of 40 studies suggested chronic cannabis use associated with poor neuropsychological performance – Authors stated that few studies met criteria to actually determine this.
- Review of 11 studies including 623 cannabis users and 409 minimal or non users failed to show effect on the neurocognitive function long term.
- Still in debate on whether cannabis has an effect on the developing adolescent brain.
- Effect on lung airflow and respiratory volumes – No association with COPD or lung cancer

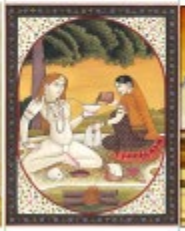
CBD

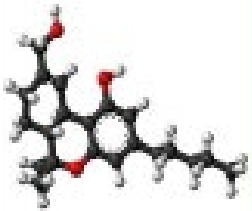
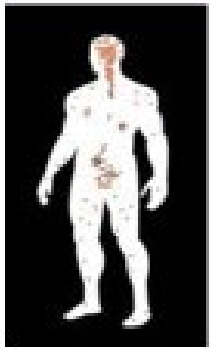
- Affects the activity of ion channels, receptors, and enzymes

- Anti-inflammatory
- Analgesic
- Anti-nausea
- Anti-emetic
- Anti-psychotic
- Anti-ischemic
- Anxiolytic
- Anti-epileptiform

3000 years of application

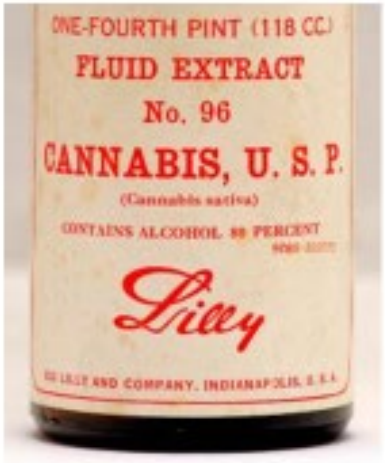
3000 years of application

2737 BC	1600 BC	800 BC	200	800
China-First evidence of medical use. Emperor Shen Nung	**India**-*Atharvaveda* First Marijuana oriented culture	**Ancient Egypt**-Holy Anointing Oil	Chinese Doctor Hua T'uo-Mixed cannabis and wine to as a surgical anaesthetic	**Arabic**-Earliest Known Compendium (9th century) of pharmacology
				

1839	1890	1964	1988	1991
Irish physician Dr. William B. O'Shaughnessy	Queen Victoria- personal prescribed Cannabis for her menstrual cramps.	THC Synthesized by Israeli scientists Raphael Mechoulam	Judge Francis Young-DEA judge concluded marijuana in natural form safest drug	Discovery of the endocannabinoid system
				

- Late 19th Century:

Cannabis-based medications were manufactured by Eli Lilly, Parke Davis and Co. (now part of Pfizer), Squibb & Sons (now called Bristol-Meyers Squibb)



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With centuries of cannabis use, what happened?

- Cannabis based medicine went out of favor in the early 20th century-With increasing use of opiates, introduction of the hypodermic needle, and the discovery of aspirin
- 1923 became illegal in Canada which is one of the first countries to make it illegal under **Opium and Drug Act**
- **Marijuana Tax Act of 1937 (USA)**

– difficult to obtain marijuana for medical purposes

– disappeared from pharmacopeias (1932 from British, 1941 from American)

- **Federal Bureau of Narcotics under Harry Anslinger**

demonized cannabis; culminated in film Reefer Madness

- Harry Anslinger Quote (1892-1975):

Most marijuana smokers are Negroes, Hispanics, jazz musicians, and entertainers. Their satanic music is driven by marijuana, and marijuana smoking by white women makes them want to seek sexual relations with Negroes, entertainers, and others. It is a **drug that causes insanity, criminality, and death -- the most violence-causing drug in the history of mankind**.

With centuries of cannabis use, what happened?

- In 1970 the Controlled Substance Act was put through by congress causing cannabis to be a schedule I drug in the US
- Schedule I drug is for drugs that have the **greatest potential for abuse with no medicinal value**
- In Canada Cannabis Act - legalization and regulation of Cannabis
  - October 17th 2018
- Both THC and CBD are under these perspective classifications

Schedule I (US)	Schedule II (US)
Cannabis	Cocaine
Heroine	Methamphetamine
LSD	Nabilone

- Schedule I Controlled Substance
- high potential for abuse
- no currently accepted medical use in treatment
- lack of accepted safety under medical supervision
- use and possession is a federal offense

Federal Restrictions on Cannabis Research

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Canada

Canada: Health Canada's role

In administering the ACMPR, Health Canada has two main roles:

- licensing and overseeing the commercial industry; and,
- registering individuals to produce a limited amount of cannabis for their own medical purposes (or to have another individual produce it for them).

Qualifying Conditions

- Cancer
- Rheumatoid Arthritis
- HIV/AIDS
- Parkinson Disease
- ALS
- Spasticity
- Multiple sclerosis, ALS, Huntington’s disease
- Epilepsy
- Seizures
- Wasting Syndrome
- Crohn’s Disease (IBD)
- PTSD
- Chronic pain

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Call for Additional Studies

- 1997: National Institutes of Health
  - Workshop on the Medical Utility of Marijuana
- 1999: Institute of Medicine
  - Marijuana and Medicine: Assessing the Science Base
- American College of Physicians
  - 2008 Position Paper: Supporting Research Into The Therapeutic Role Of Marijuana
    - stating it is “neither devoid of potentially harmful effects nor universally effective”
    - called for “sound scientific study” and “dispassionate scientific analysis” to find the appropriate balance

X5 RCT.s

Cancer pain: Largest population studied

1975 Noyes et al improved at 10mg and 20mg doses of THC compared to Placebo. Equivalent to 60mg and 120mg Codeine

- RCT Johnson 2010 showed Nabiximols (Sativex) showed pain reduction of >30% vrs placebo. Sativex (THC:CBD) superior to THC alone in cancer patients with inadequate pain management on opioid therapy.
- RCT Portenoy 2012 Sativex superior to Placebo

Cancer pain: Largest population studied

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Neuropathic Pain

Neuropathic pain

X9 RCTs

- Wade 2003
- Berman 2004
- Wade 2003
- Rog 2005

Nabiximols (Sativex) Vrs Placebo showed inconclusive results. Small sample sizes

- Nurmikko 2007

Biggest sample size of 125 showed reduction in allodynia, improved sleep, and pain scores

- Abrams 2007
- Ellis 2009
- Wilsey 2008
- Ware 2010

Inhaled THC vrs placebo showed greater pain reduction

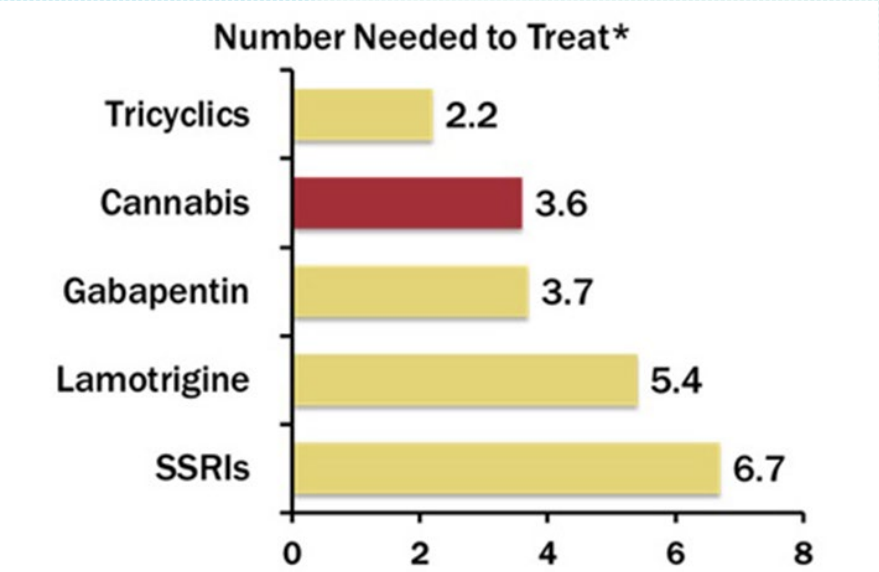

Figure 1. Common analgesics for neuropathic pain.

*to achieve a 30% reduction in pain.

Number needed to treat (NNT) = **1/(E-P)**, where E is the proportion improved in experimental condition and P is the proportion improved on placebo. Example: If 60% "improve" (according to a given definition) in the experimental condition, while 30% "improve" in the placebo condition, then NNT = 1/(.6-.3) = 3.3. Data adapted from Abrams et al. [3] and Ellis et al. [4].

Evaluated conditions

- Fibromyalgia - Nabilone
- Back pain - Nabilone
- Osteoarthritis – Nabilone
- Rheumatoid Arthritis Nabilone and THC/CBD (Sativex) Oral spray.

Primary Outcomes - based on IMMPACT and PGIC

Primary outcomes

1. Reported pain relief greater than 50%
2. PGIC much or very much improved
3. Withdrawal due to adverse events
4. Serious adverse events

Secondary

1. Reported pain relief greater than 30%
2. Sleep problems
3. Fatigue
4. Depression
5. Anxiety
6. Disability
7. Health related quality of life

Review of chronic pain associated conditions

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Fibromyalgia

Two single centered studies conducted in Canada - Diagnosis of FMS by ACR 1990 classification criteria

Ware et al 2010 – Crossover study 29/32 Nabilone with Amitriptyline

- Nabilone dose was 0.5mg to 1mg nocte
- 71 patients
- Improved sleep, did not differ from amitriptyline for effect on pain, limitation of health-relate quality of life, or mood problems.

Skrabek et 2008 – Superior pain control in daily pain

- 70 patients
- Nabilone 0.5g to 1mg bid
- Statistically significant improvements were seen in pain and anxiety and health related quality of life.

Survey of Canadian FMS patients who use Medicinal cannabis 80% use herbal

Rheumatic Arthritis

Blake et al 2006 – multicentre study in UK

- History of RA meeting ACR criteria
- Active arthritis not adequately controlled on Standard Medication
- Active drug THC/CBD oral mucosal spray Sativex: 2.7mg THC and 2.5mg CBD
- 58 patients 31 randomized to Cannabis based medicine arm.
- Statistical improvement pain on movement, pain at rest, quality of sleep
- Disease activity was significantly suppressed following Sativex treatment

Side effects

- Adverse events are not serious
- Wang et al. A system review reported MS relapse, cannabis hyperemesis syndrome, and UTI
- Non Serious
  - Dizziness, fatigue, dry mouth, nausea, euphoria, disorientation
  - Worsened short-term memory, impaired judgment and driving and appetite stimulation with weight gain

  Long-term use of cannabis in adolescents may be associated with decline in IQ

DOSING

- Titration is more clear cut with inhaled
- First time patients should start at low dose
- For inhalation slow intake and waiting several minutes between puffs
- Edible cannabis products, patients should wait 30–60 min between bites to avoid overdosing.
- Vaporization of heated cannabis creates less combustion products than smoked cannabis, and may theoretically confer less risk to cardiovascular and pulmonary function.

Spinal Pain

Pinsger 2006

- Crossover study with placebo 4 week treatment period with 4 week washout
- Nabilone phase patients reported lower spinal pain intensity compared to placebo during study but no difference at 4 week average pain intensity reduction and improvement of health –related quality of life

Migraine

- No clinical trials are currently available that demonstrate the effects of marijuana on patients with migraine headache; however, the potential effects of cannabinoids on serotonin in the central nervous system indicate that marijuana may be a therapeutic alternative.
- Ryne et al Retrospective chart review 2010 to 2014 at Marijuana Specialty clinic in Colorado.
- Positive effects were reported in 48 patients (39.7%),
- Migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($p<0.0001$) with the use of medical marijuana.
- decreased frequency of migraine headache (24 patients [19.8%]) and aborted migraine headache (14 patients [11.6%]).

Limitations

- Trials were too short
- Sample size too small

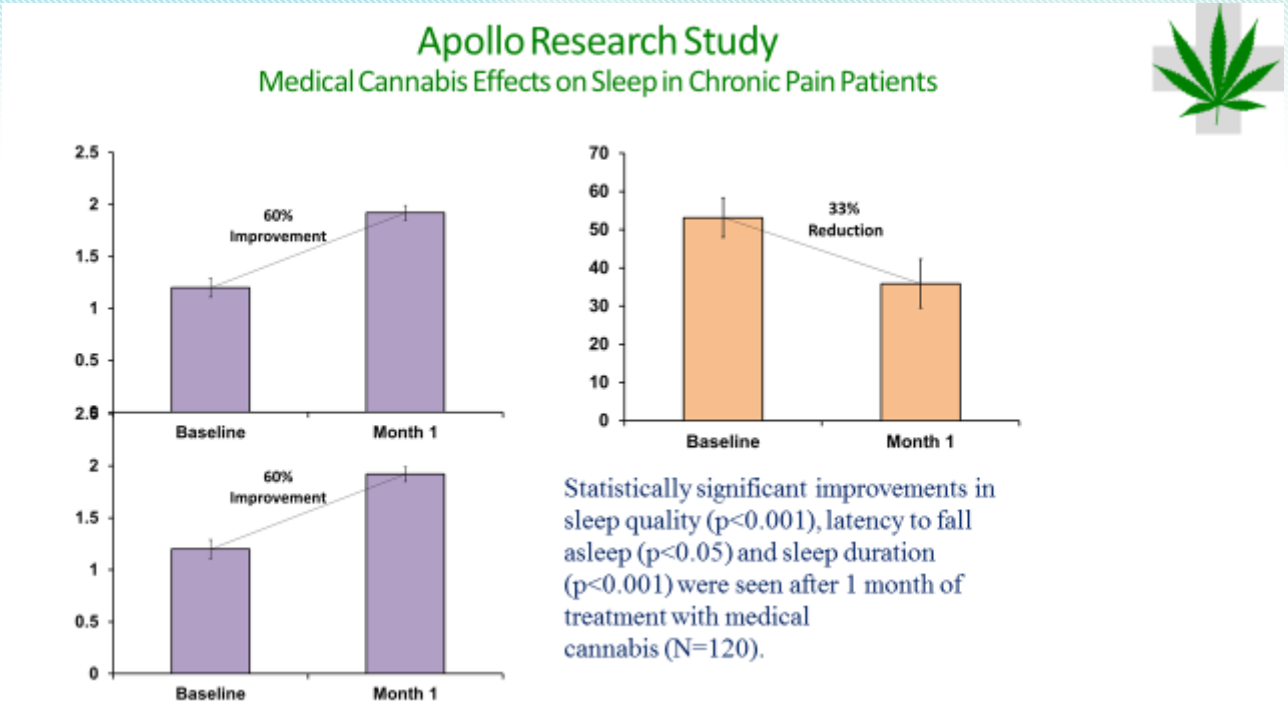
So is this only proof of concept?

Currently available synthetic cannabis medication is as good as what is already in market.

The term “Medical Marijuana” tends to lump different formulations together – important to differentiate mode of delivery, CBD and THC amount and type of plant.

Therefore distinctions must be made to ensure conclusions are not drawn more widely than justified

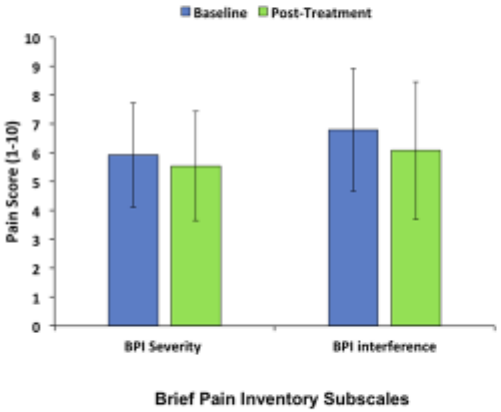
No statistically significant decreased reduction in opioid dosing?



Apollo Research Study
Medical Cannabis Effects on Sleep in Chronic Pain Patients

Apollo Research Study

Medical Cannabis Effects on Sleep in Chronic Pain Patients



A significant reduction in pain severity ($p=0.001$) and pain interference ($p<0.001$) was observed following a minimum of one month of treatment with medical cannabis (N=197). This reduction in pain scores is notable given that they occurred despite patients reducing prescription opioid use.

Medical Cannabis Effects on Sleep in Chronic Pain Patients

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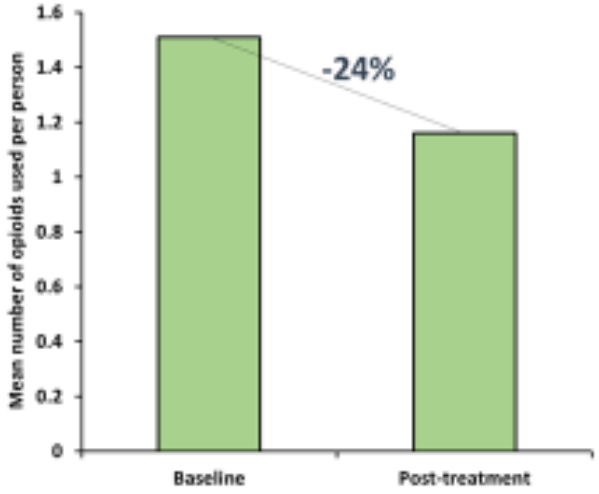
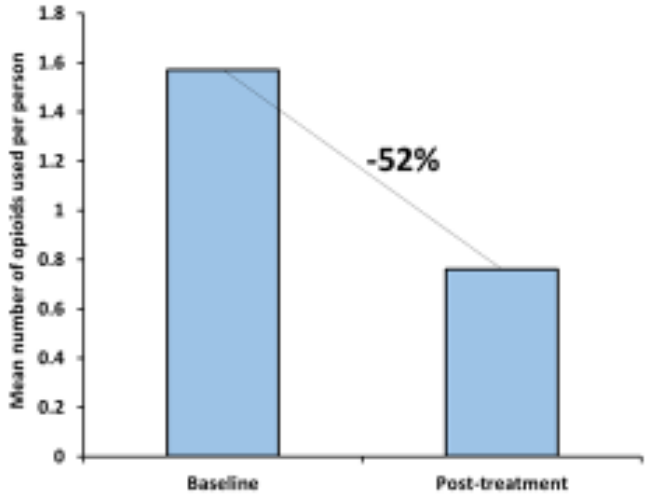
Apollo Research Study





Percent reduction in opioid use following a minimum of 1 month treatment with medical cannabis treatment. (A) Total sample (N=197) (B) Subgroup using cannabis oils only (N=47).

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Summary

- The EC system is a critical regulator of nociceptive function, active at all levels of the pain processing pathways.
- Paucity of Evidence despite the millennial use of cannabis in various forms for the management of pain
- More randomized controlled trials comparing herbal cannabis and pharmaceutical cannabinoids with established therapies are necessary to define their role in the management of chronic pain
- 1999 to 2013, 13 states in US reported 24.8% lower mean annual opioid overdose mortality rate compared to states lacking medical cannabis laws.
- Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications.


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Diagnosing neuropathic pain

- The first step in managing neuropathic pain is identifying that it is a factor.
- Usually this is by recognizing the proper clinical setting, and accompanying physical signs.
- Neuropathic pain is much more likely to develop associated with conditions that damage the nervous system, such as
  - Diabetes
  - alcohol abuse
  - zoster
  - HIV
  - Lyme disease
  - multiple sclerosis

Treatment of neuropathic pain

- Ideally, when a specific trigger is identified, treatment of the underlying disease should be initiated.
- Topical anesthetics with or without ionto- or phonophoresis may be helpful
- Regional anesthetic blocks, including sympathetic blocks, may be helpful
- These interventions are more likely to be effective if they are accompanied by aggressive physical therapy interventions.
  - Electrical stimulation, including transcutaneous electrical nerve stimulation
  - acupuncture-like stimulation
  - spinal cord stimulation
  - activation of local receptors by mobilization and massage.
  - direct stimulation of painful areas may be poorly tolerated.
- In these cases, stimulation of adjacent areas, or even treatment of the opposite side of the body may be quite useful.
  - may be useful in helping the person tolerate local therapy in the area of pain.

Table 1: Screening and assessment tools to help differentiate neuropathic pain (NP) from non-NP

Tool	Components	Additional information
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[21]	Patient symptom self-assessment Physical exam signs measured by healthcare professional	Translated and validated in several languages Not quantitative S-LANSS (self-report LANSS test) is a modified version that allows patient to perform physical exam
Neuropathic Pain Questionnaire (NPQ)[22]	Self-reported assessment	Translated and validated in several languages Only tool to incorporate symptoms related to weather changes Not quantitative NPQ-SF is a short-form version
Douleur Neuropathique 4 Questions (DN4)[23]	Symptoms and physical exam signs	Translated and validated in several languages Not quantitative One of the few to incorporate itch
painDETECT[24]	Patient symptom self-assessment	Translated and validated in several languages Includes radiation of pain in the assessment Not quantitative Not as predictive of NP in certain painful conditions
ID Pain[25]	Patient symptom self-assessment	Translated and validated in several languages Available to use for free Short and easy to use Not quantitative
Standardized Evaluation of Pain (StEP)[26]	Symptoms and physical exam signs	Highest accuracy in diagnosing low back pain compared to others in this chart Not quantitative Can be completed in 10-15 minutes

Treatment of neuropathic pain

- Neuropathic pain is much more likely to be described a shooting, stabbing, burning, or searing, and it's often worse at night.
  - A potential distinction from most muscular pain.
  - Distinct from inflammatory pain, which tends to be worse first thing in the morning, and during activity.
- Neuropathic pain is often worse at night:
  - Because lack of normal input to the nervous system
  - Circadian rhythms in pain thresholds.
- The distribution of pain can help identify neuropathic pain.
- Peripheral etiologies, symptoms often follow the route of the damaged peripheral nerve or nerve root (such as in cases of sciatica).
- Central etiologies, symptoms often involve large areas of the limb or body region.
  - May be changes in skin color, temperature or texture in the area.
  - May also be other evidence of damage to the nervous system (which may help to define a cause).
  - Greater variety of pain related phenomena, including dysesthesias (painful paresthesias) and allodynia (pain generated by an innocuous stimulus)
  - More likely to be autonomic changes.

Treatment of neuropathic pain

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- Unfortunately, nerve destructive procedures, which may be helpful on occasion, can worsen or even contribute to neuropathic pain.
- Various systemic treatments have been helpful
  - Certain anticonvulsants that calm abnormal nerve activity antidepressants that enhance serotonin and norepinephrine in the nervous system.
- Opiates may actually result in further sensitization of neural pathways over the long run.
  - Should only be used in full recognition of this potential.
  - Though some individuals are more susceptible to this sensitization, it is not clear how to identify them.

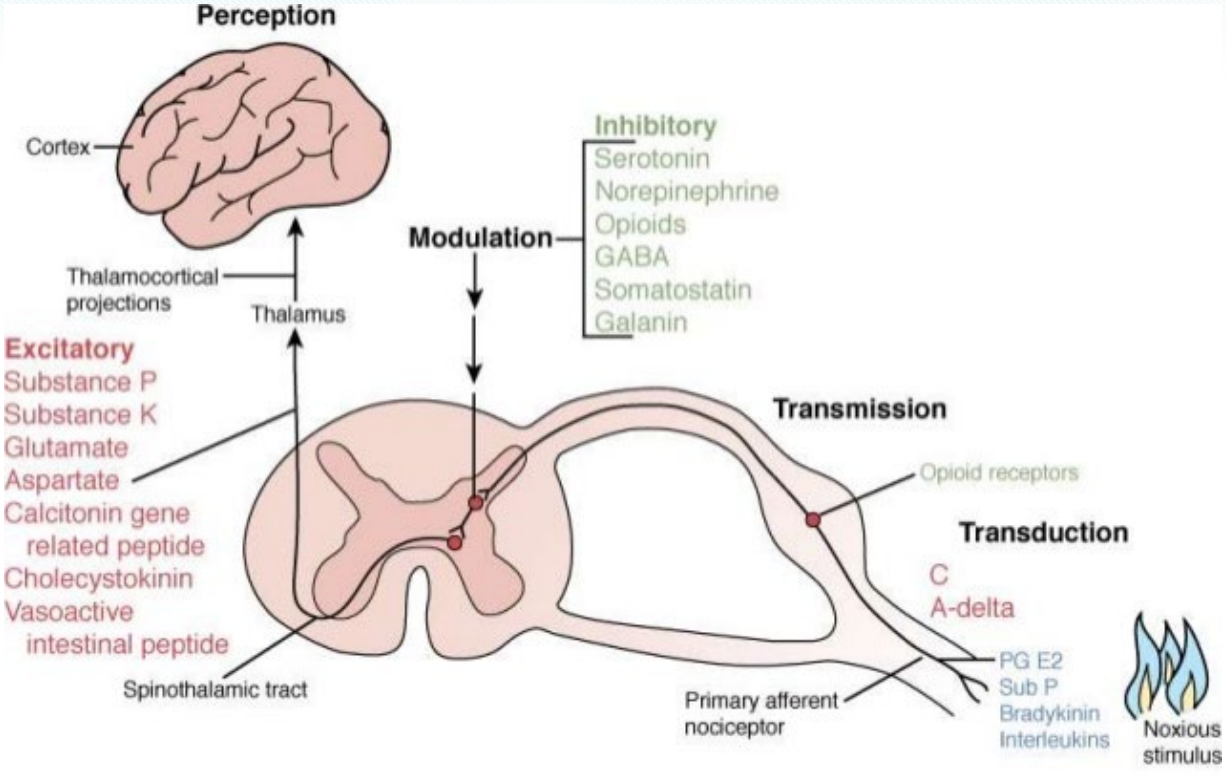

Table 2. Doses and adverse effects of select medications used for the treatment of neuropati

Medication	Dosing		Common adverse effect(s)	Major adverse effe
	Initial	Effective		
Calcium channel α2-delta ligands				
Pregabalin[38]	150mg/day, given in either two or three divided doses Dose may be increased to 300mg/day after an interval of three to seven days[38]	300–600mg/day[38]	Somnolence, peripheral oedema, weight gain	Angioedema, hepatotoxicity, rhabdomyolysis, su thoughts and beha seizures with rapid discontinuation, thrombocytopenia
Gabapentin[39]	Day 1 — 300mg once daily Day 2 — 300mg twice daily Day 3 — 300mg three times daily[39]	900–3,600mg/day[39]	Sedation, peripheral oedema, weight gain	Drug rash with eosinophilia and systemic symptom (DRESS), suicidal thoughts and beha seizures with rapid discontinuation

Antidepressants – TCA				
Amitriptyline[40]	10–25mg/day Dose can be increased 10–25mg every three to seven days as tolerated[40]	25–75mg/day Doses above 100mg should be used with caution[40]	Somnolence, anticholinergic effects (e.g. xerostomia, urinary retention, constipation, blurred vision, mydriasis), fatigue, weight gain	Cardiac abnormalit heart failure exacerbation, QT prolongation, stroke seizures, hepatotox bone marrow suppression, suicid thoughts and beha mania or hypomani patients with bipola disorder, neurolepti syndrome, serotoni syndrome, severe hyponatremia, frag bone fractures
Nortriptyline[41] * **	25mg/day then gradually adjust levels to therapeutic benefit[41]	75–100mg/day Manufacturer does not recommend >150mg/day[41]		
Desipramine[42] * **	25mg at bedtime, then increase in increments of 25mg daily every three to seven days to desired effect[42]	Max dose 150mg/daily[42]		

Antidepressant – SNRI				
Duloxetine[28],[43]	20–30mg/day[28] or 60mg/day[43] titrate up to 60mg twice a day	60–120mg/day in divided doses[28],[43]	Nausea, drowsiness, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia	Stevens-Johnson syndrome, hepatotoxicity, hypertensive crisis, gastrointestinal haemorrhage, delir myocardial infarctic cardiac arrhythmia glaucoma, suicidal thoughts and beha mania or hypomani patients with bipola disorder, seizures, severe hyponatrae fragility bone fractu neuroleptic syndro serotonin syndrom
Venlafaxine[44] * **	37.5mg or 75mg each day. Increase by 75mg weekly until desired effect (max dose of 225mg/daily)[44]	75–225mg/day[44]	Nausea, drowsiness, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia	

Topical/local treatment				
Lidocaine 5% plaster[45] ***	One to three patches for up to 12 hours applied to the painful area in a 24-hour period[45]	One to three patches for up to 12 hours applied to the painful area in a 24-hour period[45]	Local erythema, rash, itch at application site	
Capsaicin 8%[46]	One to four patches applied to the painful area, repeat every three months[46]	One to four patches applied to the painful area, repeat every three months[46]	Pain, erythema, itch, oedema, vesicles, dryness at application site	Transient increase blood pressure ma occur during and a treatment
Botulinum toxin type A[47] * **	Individualise dosage according to response. May repeat every three months[47]		Pain at injection site	

Opioids				
Tramadol[48],[88] * **	50mg/daily; increase weekly by 50mg/day[88]	50–100mg four times daily or 100–400mg daily (controlled release)[88]	Drowsiness, nausea, vomiting, constipation, light-headedness, dizziness, headache	Confusion, seizure cardiac arrhythmia hypertension, Stev Johnson syndrome
Tapentadol[49] *	Extended release: 50mg, twice daily; may increase by 50mg/day every three days to a range of 100–250mg twice daily[49]	Extended release 50mg, twice daily[49] Extended release: 100–250mg, twice daily[49]	Drowsiness, nausea Vomiting, constipation, dizziness	Respiratory depres serotonin syndrom Seizures, hyperten neonatal opioid withdrawal syndro

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Table 3. Recommended first- and second-line pharmacologic agents for general peripheral neuropathic pain from selected organisations

Therapy	National Institute for Health and Care Excellence (NICE)[18]	Canadian Pain Society (CPS)[87]	Neuropathic Pain Special Interest Group (NeuPSIG)[50]
	UK	Canada	International
	Published 2013, updated 2017	Published 2014	Published 2015
First-line pharmacotherapy	Amitriptyline Duloxetine Gabapentin Pregabalin	Gabapentin Pregabalin Tricyclic antidepressants (TCAs) Serotonin norepinephrine reuptake inhibitors (SNRIs)	Gabapentin Gabapentin XR or enacarbil Pregabalin SNRIs-duloxetine or venlafaxine* TCA**
Second-line pharmacotherapy	Capsaicin cream Short-term tramadol for acute rescue only***	Tramadol Controlled-release opioids	Tramadol Capsaicin 8% patch**** Lidocaine patch
Third-line pharmacotherapy		Cannabinoids	
Fourth-line pharmacotherapy		Topical lidocaine	

*Duloxetine is the most studied SNRI and, therefore, recommended.

**Doses ≥75mg of amitriptyline, imipramine or dopamine are not recommended for patients ≥65 years.

***Long-term use of tramadol should not be used in non-specialist settings unless advised by a specialist.

****Long-term safety of repeated applications of high-concentration capsaicin patches has not been established.

Table 4. Recommended pharmacologic agents for specific peripheral neuropathic pain cond organisations

Specific neuropathic pain conditions	National Institute for Health and Care Excellence (NICE) [18]	Canadian Pain Society (CPS) [87]	American Academy of Neurology (AAN) [76]	American Diabetes Association (ADA)[28]
	United Kingdom	Canada	International; United States	United States
	Published 2013, updated 2017	Published 2014	Published 2011, reaffirmed 2016	Published 201
Trigeminal neuralgia	First-line: Carbamazepine	First-line: Carbamazepine Second-line: Topical lidocaine		
Diabetic neuropathic pain			Level A: Pregabalin Level B: Venlafaxine Duloxetine Amitriptyline Gabapentin Valproate Opioids Capsaicin Isosorbide nitrate spray	Level A: Pregabalin Duloxetine Level B: Gabapentin TCAs
Chemotherapy-induced neuropathic pain				

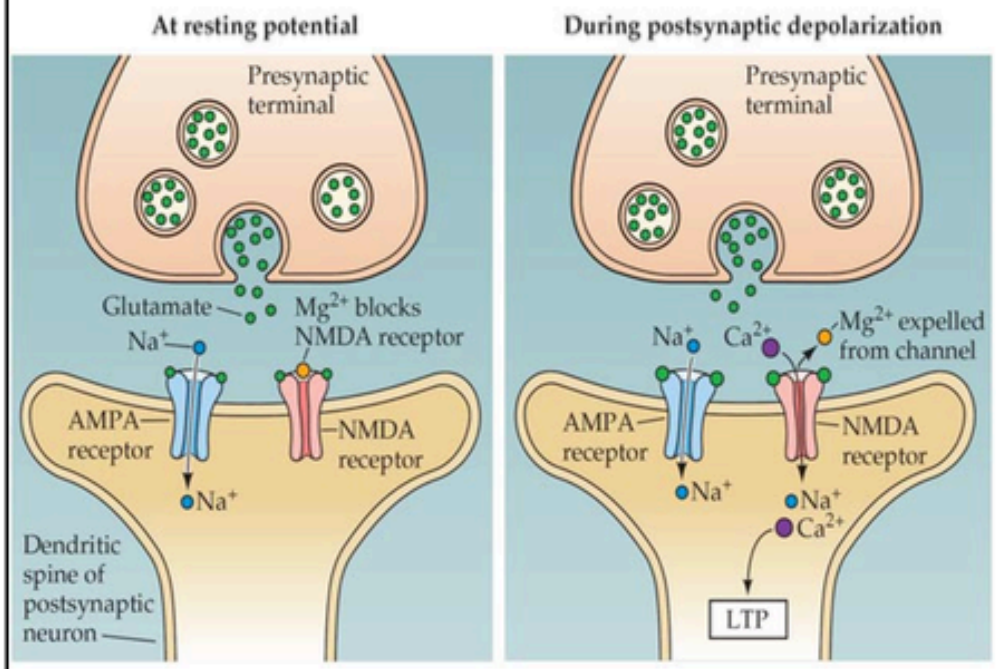

Figure 2: Short-term vs. long-term potentiation. If the post-synaptic cell is at resting potential, solely a short-term potentiation is induced. Due to the magnesium ion block of the NMDA receptor only AMPA receptors are activated. However, if the post-synaptic cell is depolarized, both AMPA and NMDA receptor are activated and there is calcium ion influx into the cell. This leads to the induction of long-term potentiation. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartic acid; LTP, long-term potentiation. (Purves *et al.*, 2004)

- Lidocaine and ketamine infusions help with the acute pain as well as central sensitization
- Can be offered in pre-operative, intra-operative, post-operative and outpatient settings.
- Used to help decrease the potentiation of chronic pain and increase susceptibility to additional pain modalities
- In addition to neuropathic pain has encouraging research on depression
- Allevio is conducting a prospective clinic trial on lidocaine + ketamine infusions for neuropathic pain.
- An enantiomer of ketamine, S-ketamine (esketamine) has been recently approved by the FDA for depression.

Spravato™ (esketamine) C III
nasal spray

SPRAVATO™ is
Now Approved

SPRAVATO™ is a prescription medicine, used along with an antidepressant taken by mouth, for treatment-resistant depression (TRD) in adults.

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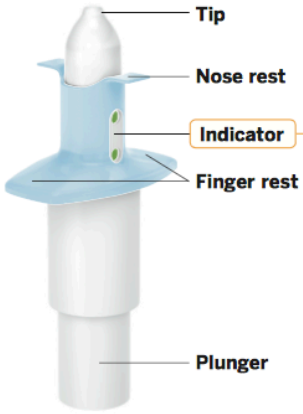
Table 1: Recommended Dosage for SPRAVATO

		Adults
Induction Phase	**Weeks 1 to 4:**	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	**Weeks 5 to 8:**	
	Administer once weekly	56 mg or 84 mg
	Week 9 and after:	
	Administer every 2 weeks or once weekly*	56 mg or 84 mg

Nasal Spray Device

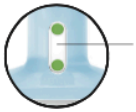


Each device delivers two sprays containing a total of 28 mg of esketamine.

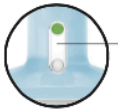
Indicator

One device contains 2 sprays. (1 spray for each nostril)

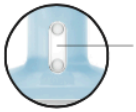
2 green dots (0 mg delivered)



1 green dot



No green dots
Two sprays (28 mg) delivered



Step 1 Get ready

Before first device only:

Instruct patient to blow nose **before first device only**.

Confirm required number of devices.

56 mg = 2 devices
84 mg = 3 devices

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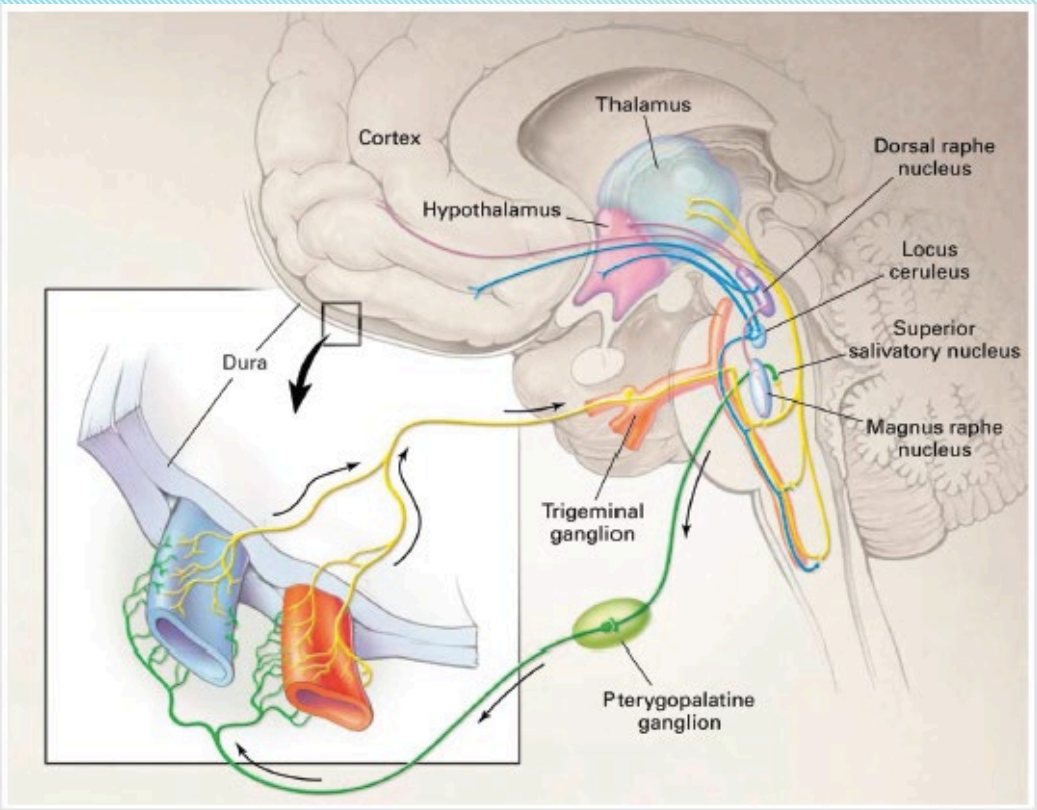
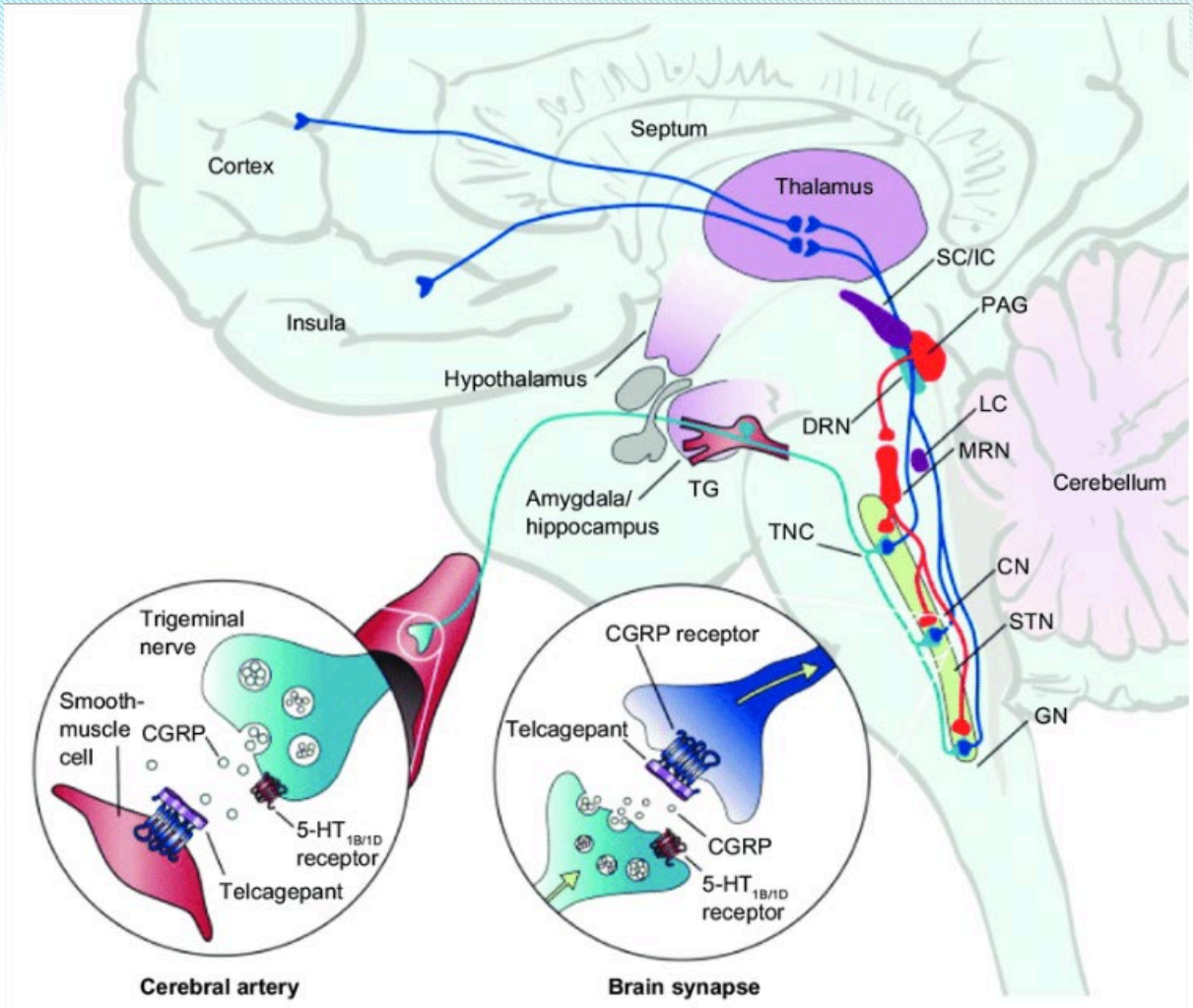
Neuropathic pain patients symptoms

- Behavioral therapy is very important in chronic pain
  - Stress amplifies pain and relaxation can reduce excitability of the autonomic nervous system.
- Sleep is quite abnormal in neuropathic pain patients, who have particularly disrupted slow-wave sleep.
  - Various sleep interventions may be useful in these patients.



GURE 1-1 Pathophysiology of migraine. Migraine involves dysfunction of brainstem pathways that normally modulate sensory input. The key pathway for the pain is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex. In turn, these neurons project through the trigeminothalamic tract, and, after decussating in the brainstem, form synapses with neurons in the thalamus. A reflex connection exists between neurons in the pons and neurons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal autonomic reflex is present in people who do not experience migraines and is expressed most strongly in patients with trigeminal autonomic cephalalgias, such as cluster headache and paroxysmal hemicrania; it may be active in migraine. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus.



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- In addition to the aforementioned neuropathic agents which may also be used in migraines, CGRP inhibitors are now available on the market
- The first of such medications to be available in Canada is Amovig.
- It’s a monthly injection that can be used for both episodic and chronic migraines.

Aimovig

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Magnesium for Migraine

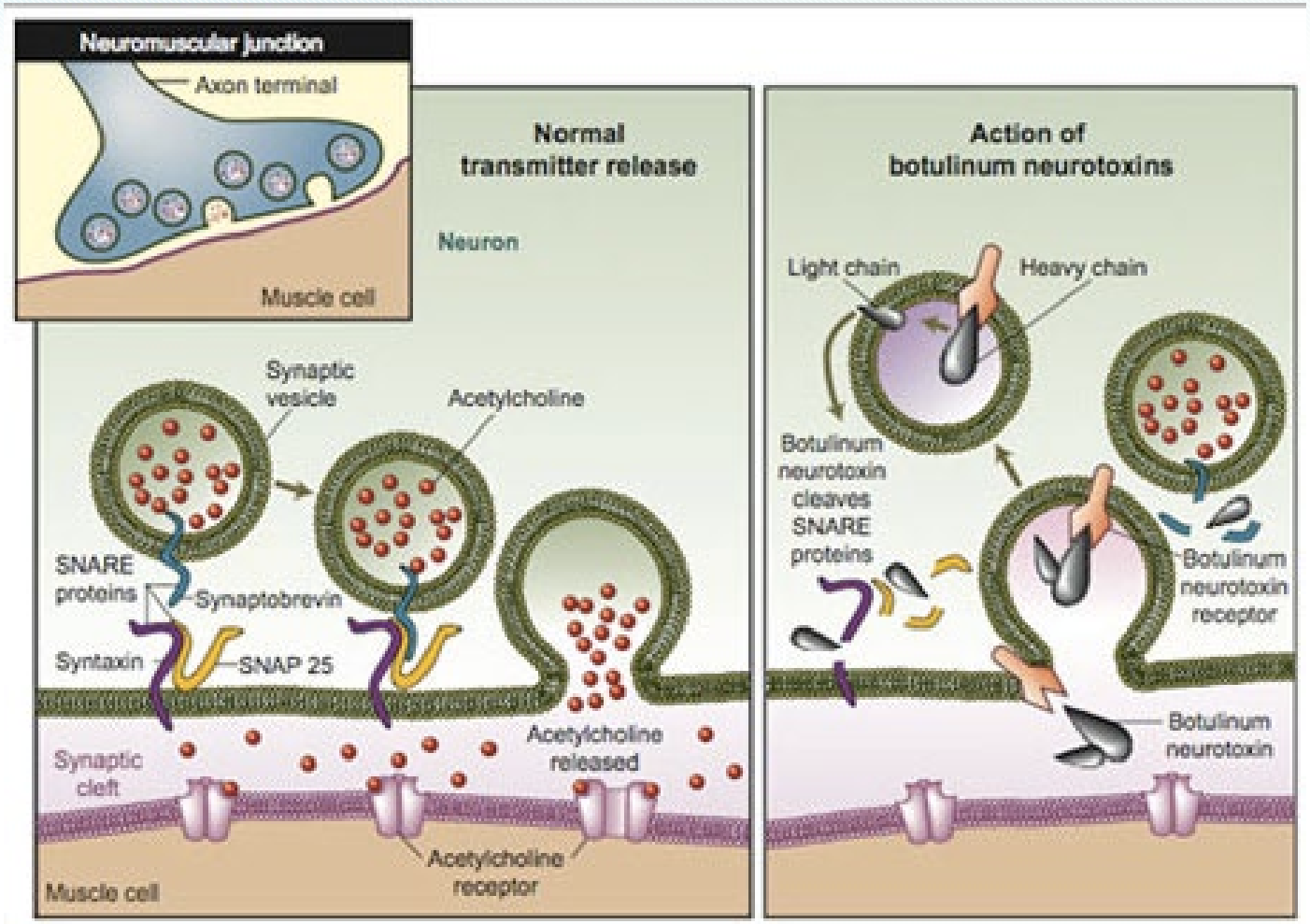
- Migraine patients with aura have a lower amount of magnesium in their CSF
- Magnesium oxide is frequently used in pill form to prevent migraine.
  - Dose of 400-500 mg per day
  - Pregnancy Category A
- Magnesium can be given for acute migraines intravenously as magnesium sulfate at 1-2 gm over 15-45 minutes based on tolerability.

Botox

- OnabotulinumtoxinA FDA approved for chronic migraine, defined as > 15 headache days/month, with > 4 headache hours/day.
- After 1st injections effects delayed or transient. So a 2nd set is warranted before deeming failure.
- Doses 155 units fixed sites - 195 units for fixed & follow-the-pain sites
- Repeat Q3 months

Botox

- 7 botulinum toxin serotypes are produced by Clostridium botulinum (i.e., A, B, C, D, E, F, and G).
- Heavy chain of 100 kDa and a light chain of 50 kDa linked by 1 disulfide bond and are synthesized as inactive single-chain polypeptide.
- Proteolytic cleavage of neurotoxin to heavy and light chains results in activation.
- Heavy chain binds to nerve terminals -> endocytosis -> light chain activated
- Neurotransmitters in vesicles, fuse with presynaptic membranes, releasing neurotransmitters into the synaptic cleft.
- Process mediate by soluble N-ethyl-maleimidesensitive factor (SNARE) proteins.
- Light chain cleaves the SNARE proteins and prevents vesicular fusion



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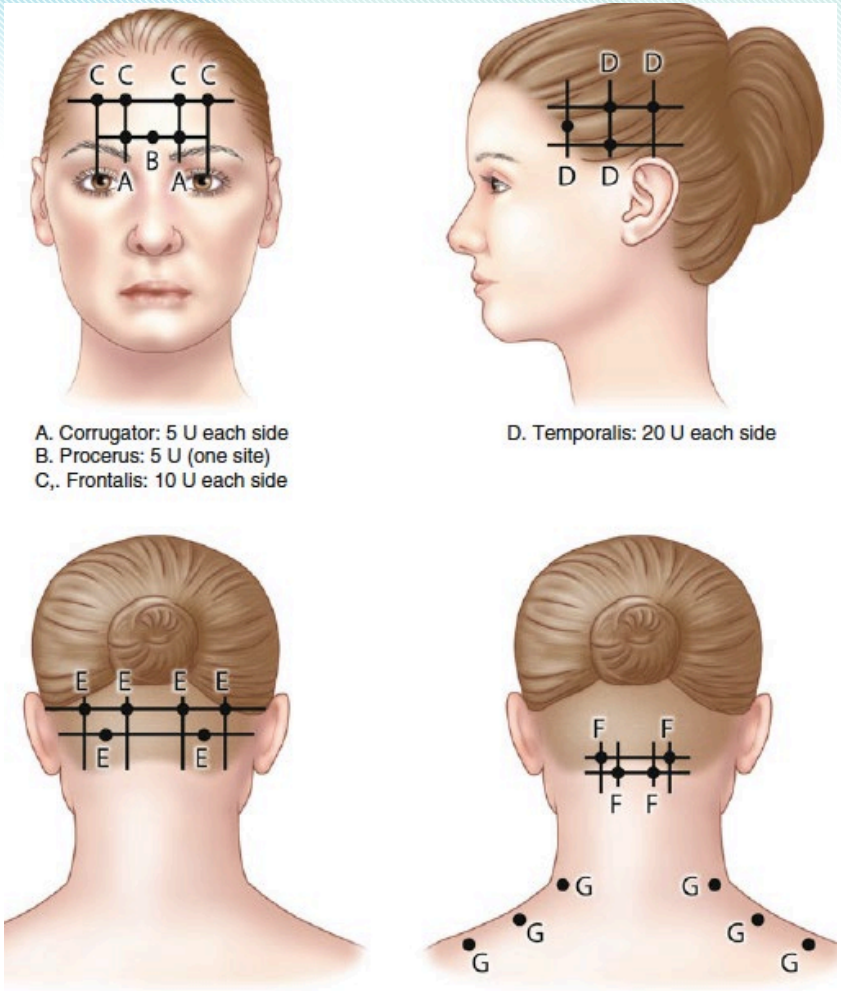
Botox

- Onabotulinum toxin A inhibits pain by preventing peripheral sensitization in a dose-dependent manner.
- Onabotulinum toxin A blocks injury-induced mechanical allodynia, neuronal activation, and changes in gene expression, even far from the injection site
- Blocks microglia activation; a decrease in glial and macrophage activation may be important for the long-lasting effect of on chronic pain



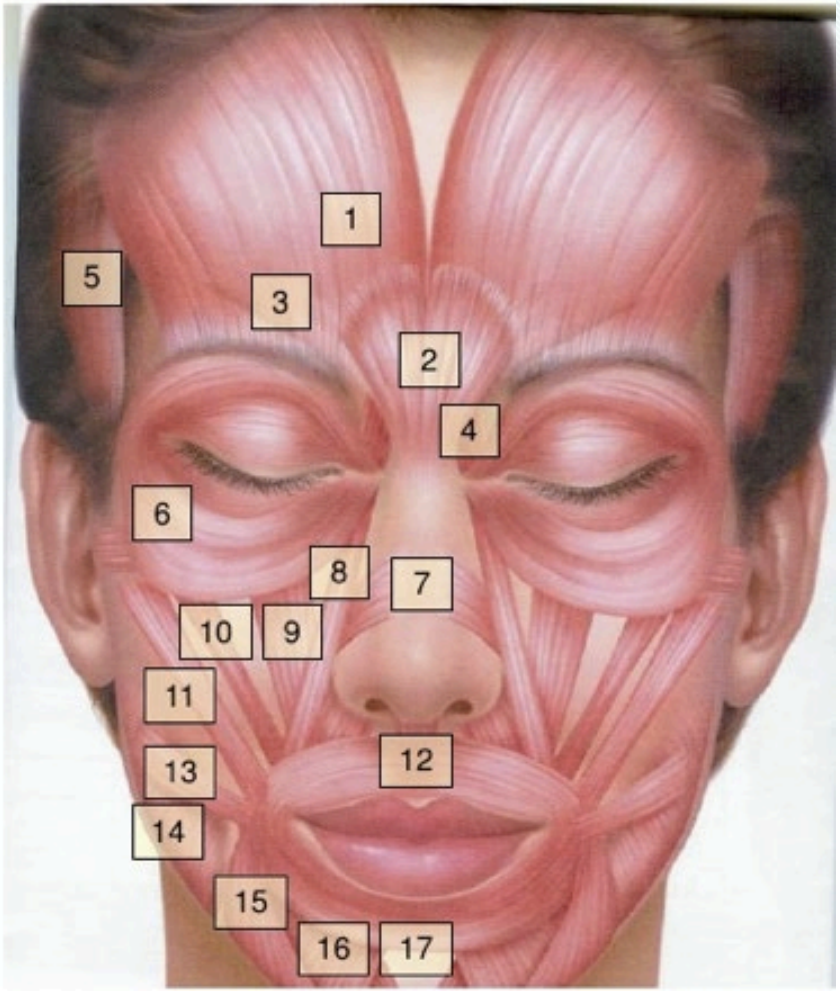
A. Corrugator: 5 U each side
B. Procerus: 5 U (one site)
C,. Frontalis: 10 U each side

D. Temporalis: 20 U each side

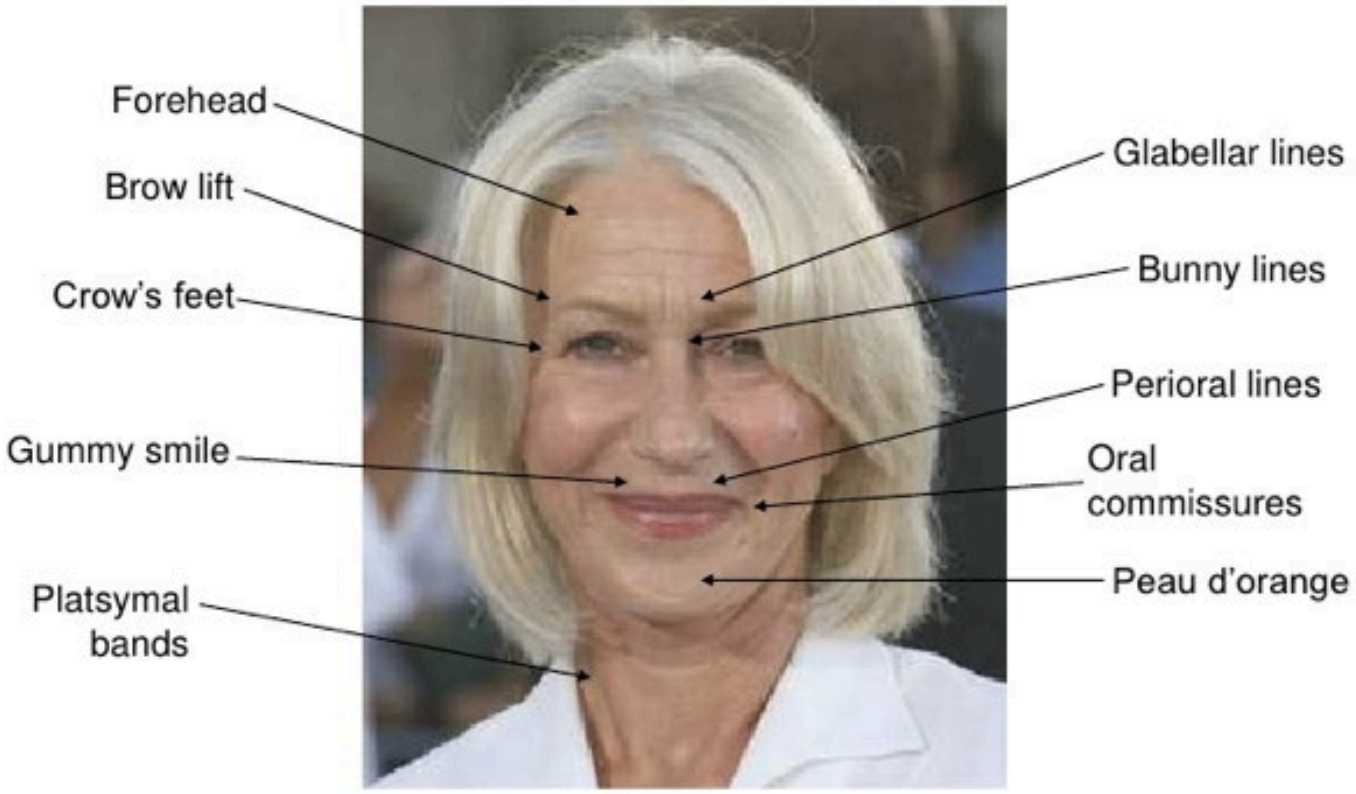
E. Occipitalis: 15 U each side

F. Cervical paraspinal:
10 U each side
G. Trapezius: 15 U each side

1. Frontalis
2. Procerus
3. Corrugator supercilli
4. Depressor supercilli
5. Temporalis
6. Obicularis oculi
7. Nasalis
8. Levator labaii superioris alaeque nasi
9. Levator labaii
10. Zygomaticus minor
11. Zygomaticus major
12. Obicularis oris
13. Modeolus
14. Masseter
15. Depressor anguli oris
16. Depressor labii
17. Mentalis



Facial Areas Commonly Treated with BoNT-A



Thank You

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