Get a Leg Up on Musculoskeletal Pharmacology

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Disclosures

I have no personal or financial interests to declare.

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What we will NOT cover:

1. acetaminophen
2. NSAIDS
3. COX-2 Inhibitors
4. Opioids
5. Anti-convulsants

Outline

Oral Agents

- glucosamine/chondroitin
- seratonin/norepinephrine re-uptake inhibitors (SNRIs)
- muscle relaxants

Topicals

- lidocaine
- capsaicin
- diclofenac

Injections

- glucocorticoids
- hyaluronic acid
- platelet rich plasma

Glucosamine & Chondroitin

Should glucosamine/chondroitin be used for the treatment of degenerative joint disease (osteoarthritis)?

UTD: *"due to…contradictory and…uncertain data, glucosamine & chondroitin are not endorsed by OA guidelines developed by professional organizations*"

Glucosamine & Chondroitin

Glucosamine

- derived from shrimp/crab/lobster shells
- listed as “chrondroprotective agent”??
- caution in patients with shellfish allergy?

Chondroitin

- derived from shark, cattle cartilage
- inhibits degradative enzymes??

Glucosamine & Chondroitin

- favorable safety profile, but…
- UpToDate: high quality trials have shown ***little to no evidence of benefit***

Glucosamine & Chondroitin

- placebo effect?
  - analgesic only
  - does not heal or re-grow cartilage!
- supplement – not regulated by the FDA
- some studies show ~70% improved pain

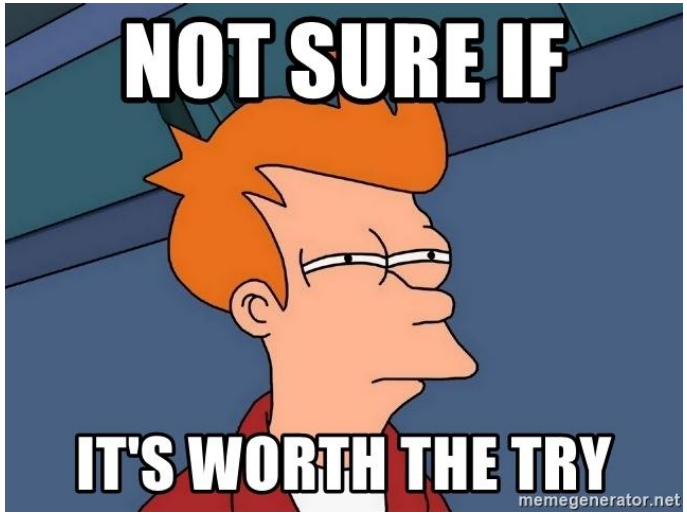
Glucosamine & Chondroitin

- Recommendations?
  - little side effects
  - try anything conservative before TKA?
  - one study: synergistic with NSAIDS

  - does based on the glucosamine: 1,500mg per day

Glucosamine & Chondroitin

Should glucosamine/chondroitin be used for the treatment of degenerative joint disease (osteoarthritis)?



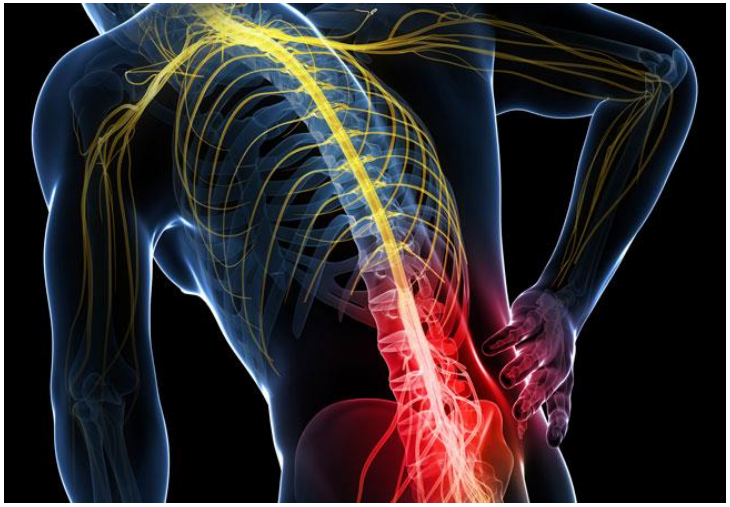
SNRIs

- typically known as anti-depressants
  - analgesic effects separate from anti-depressant effects

- Examples:
  1. venlafaxine (Effexor)
  2. desvenlafaxine (Pristiq)*
  3. duloxetine (Cymbalta)

SNRIs

- more specifically…
  - venlafaxine: “chronic pain syndromes”
  - duloxetine: “fibromyalgia & chronic MSK pain”



SNRIs

- Indicated for chronic pain even in the absence of depression
  - especially good for LBP that has been unresponsive to non-pharmacologic therapy

SNRIs

- Common Side Effects:
  - constipation
  - nausea**
  - fatigue
  - dizziness
  - dry mouth

SNRIs

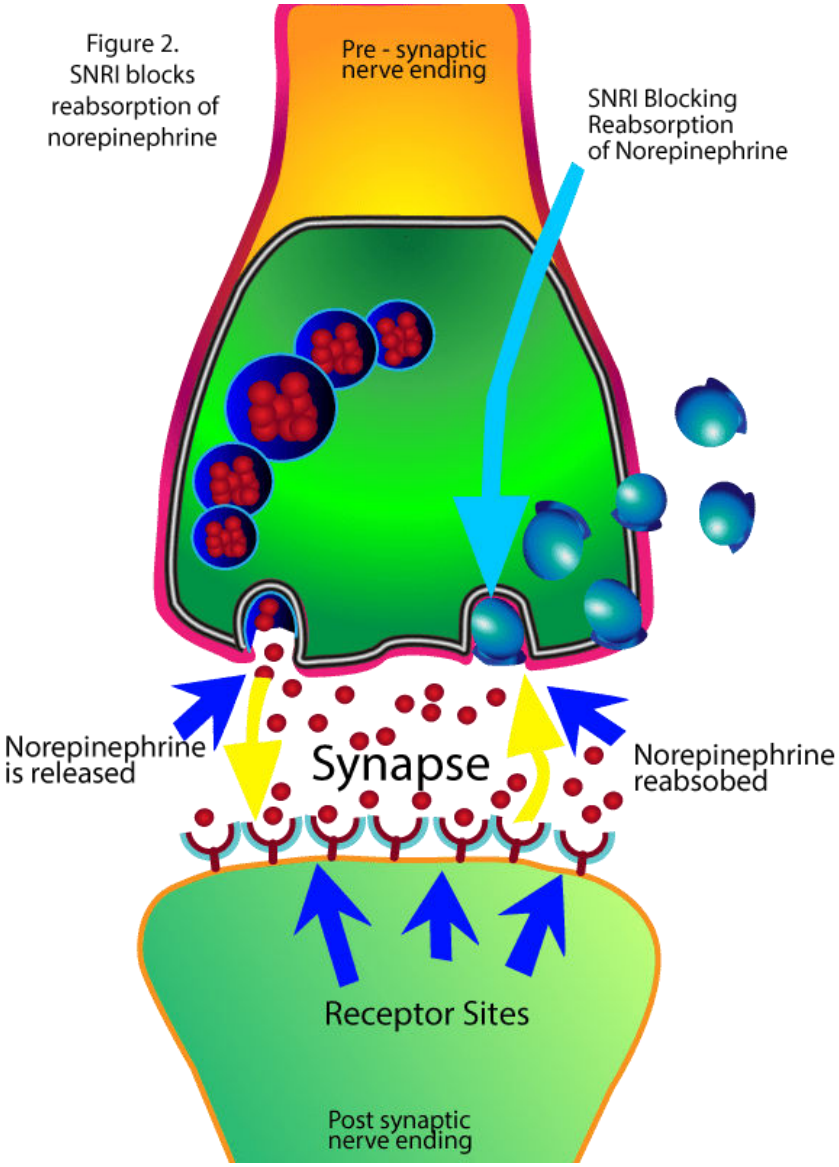
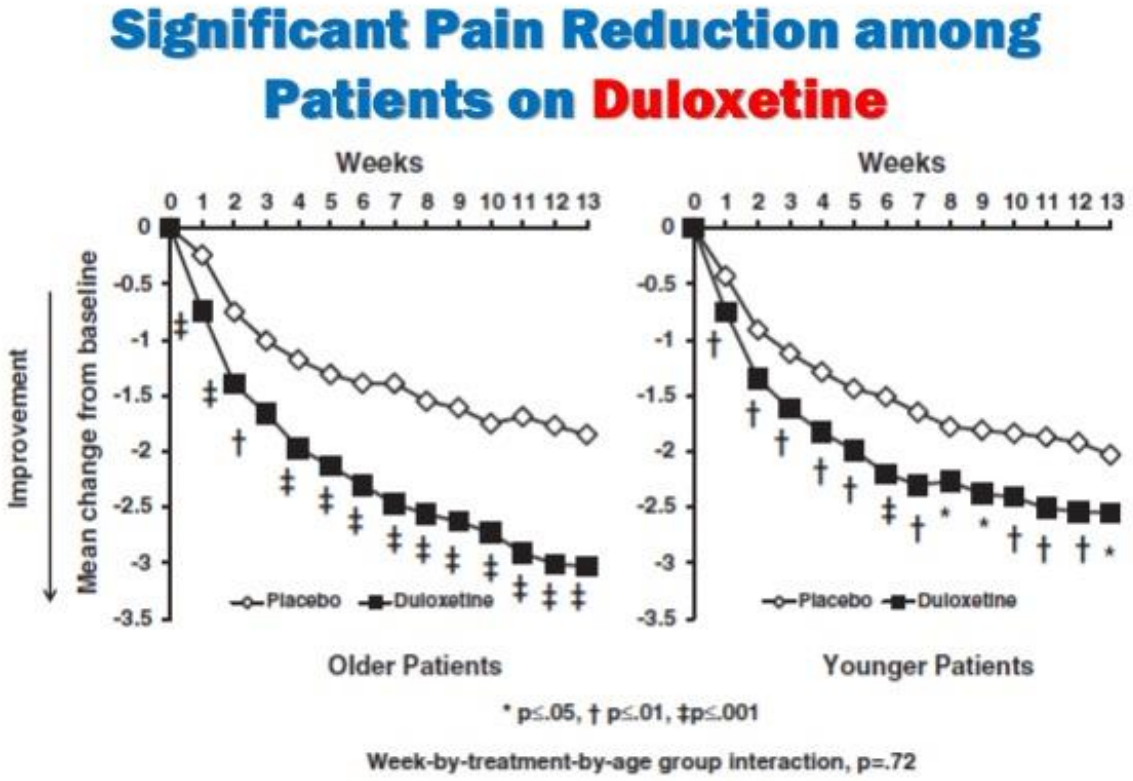


Figure 2.
SNRI blocks
reabsorption of
norepinephrine
Pre - synaptic
nerve ending
SNRI Blocking
Reabsorption
of Norepinephrine
Norepinephrine
is released
Synapse
Norepinephrine
reabsobed
Receptor Sites
Post synaptic
nerve ending

SNRIs



Micca JL, et al. Safety and efficacy of duloxetine treatment in older and younger patients with OA knee pain: a post hoc, sub-group analysis of two randomized placebo controlled trials. BMC Musculo Dso 2013; 14:137.

SNRIs

- Noticeable differences in pain may require 2-4 weeks of therapy
  - failures due to **too low a dose** and/or **too short of a trial**

- Dosing:
  - duloxetine (immediate release): 60mg – 120mg, daily
  - venlafaxine (extended release): 75mg – 225mg, daily

SNRIs

- Note that we've been talking about **SNRIs**!
- Evidence for **SSRIs** treating MSK pain is non-existent

Muscle Relaxants

- Examples:
  1. cyclobenzaprine (Flexeril)
  2. metaxalone (Skelaxin)
  3. carisoprodol (Soma)
  4. methocarbamol (Robaxin)

Muscle Relaxants

- True: many painful conditions may arise from painful muscles, including muscle spasm, but…

…no evidence that ‘muscle relaxants’ directly relax muscles

Muscle Relaxants

- Of the four examples provided:
  - None act directly on the muscle itself
  - Any relief is likely related to sedation, not analgesic effect

- When true **muscular spasticity** is present (i.e., with cerebral palsy, multiple sclerosis, post-stroke), then **anti-spastic** drugs are indicated
  - baclofen
  - tizanidine (Zanaflex)

Muscle Relaxants

Important Caveat:

1. cyclobenzaprine (Flexeril)
2. metaxalone (Skelaxin)
3. carisoprodol (Soma): no longer recommended for any indication!
4. methocarbamol (Robaxin)

Muscle Relaxants

- cyclobenzaprine (Flexeril) is indicated for mild to moderate fibromyalgia
  - but only FDA approved for **short-term** use
  - mechanism is **unrelated to muscle relaxation** (chemically, it is a tricyclic that resembles amitriptyline)

- cyclobenzaprine (Flexeril) and tizanidine (Zanaflex)
  - these two have been studied the most for **acute LBP**
  - but not much evidence for **chronic LBP**

Muscle Relaxants

Summary

1. Do not use carisoprodol (Soma) at all

2. If true spasticity: use anti-spastic like baclofen or tizanidine (Zanaflex)

3. If mild-to-moderate fibromyalgia, try cyclobenzaprine (Flexeril), but only short-term

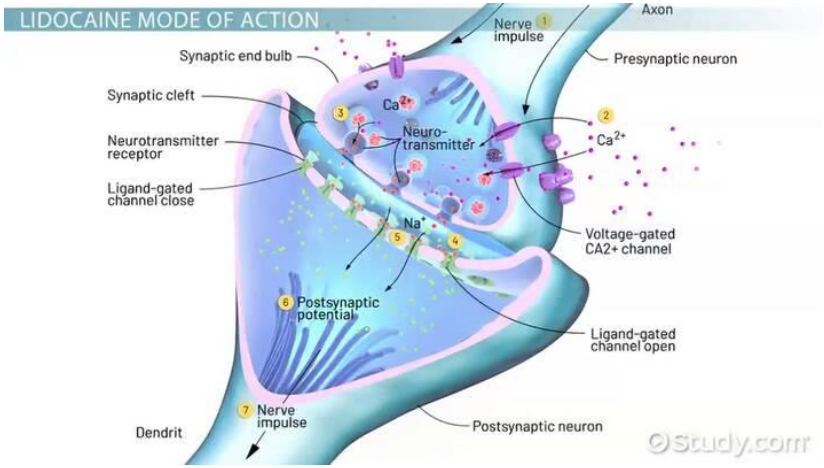
4. If acute LBP, try cyclobenzaprine (Flexeril) or tizanidine (Zanaflex), but not for chronic LBP

Muscle Relaxants

- All of them have anticholinergic properties
  - may cause CNS depression
  - caution in elderly
  - caution when combined with other CNS depressants

Topical lidocaine

- Pharmacology: stabilizes neuronal membrane by inhibiting ionic fluxes required for the initiation & conduction of impulses



Topical lidocaine

- A topical anesthetic
- Available as gel, cream, patch, spray, ointment, lotion, etc.
- Strengths: anywhere from 1-5%

- Indications:
  - neuropathic pain
  - chronic pain

Topical lidocaine

- Rx Patch
  - a single 5% patch contains 700mg of lidocaine
  - can apply BID
  - max 3 patches at once…if so, leave a patch free period of 12-hours

- Systemic absorption is low (~3%)

Topical lidocaine

- Effectiveness??

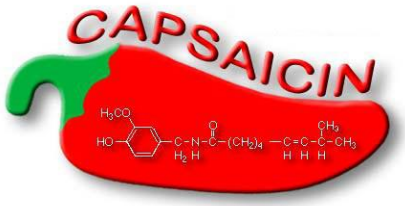
- UpToDate:
  - "data supporting the efficacy…is limited. The best evidence suggests…may be beneficial for **post-herpetic neuralgia** and painful **diabetic neuropathy**"

  - most appropriate for patients with **localized** neuropathic pain

  - Although can be used as monotherapy, is often used as an **adjunct to systemic medication**

Topical capsaicin

- 1878: chemical was first isolated from chili peppers
- 1930: structure was chemically synthesized



- similar to “pepper spray”

Topical capsaicin

- High or repeated doses of capsaicin induce initial pain sensation that is followed by analgesia (Fattori, 2016)

- topical counter-irritant
  - gate control theory

- depletes substance P from sensory neurons

Topical capsaicin

- May take 2 weeks of daily use before effects are noticed
  - and 6-8 weeks for full effect
  - therefore, not effective for acute pain

- Strengths: 0.025%, 0.035%, 0.075%, 0.1%
- Applied 3-4x per day

Topical capsaicin

- Most effective on superficial joints
  - UE: hands, wrists, elbows
  - LE: knees, ankles, feet
- Useful in patients who cannot tolerate oral NSAIDS
  - patients with degenerative joint disease (osteoarthritis)

Topical capsaicin

- Side Effects: localized burning sensation
  - do not use on mucous membranes

- Precautions:
  - Ingested? nausea, vomiting, abdominal pain, diarrhea
  - Eye exposure? tearing, pain, blepharospasm

Topical capsaicin

- Alternative uses:
  - post-herpetic neuralgia
  - diabetic neuropathy
  - HIV neuropathy

- UpToDate:
  - Several RCTs investigating topical capsaicin for **knee OA**
  - "In most studies, topical capsaicin was superior to placebo…**33% pain reduction after 4-weeks**"

Topical diclofenac

- A topical NSAID
- Available as gel or patch

Voltaren Gel 1.0%	Flector Patch 1.3%
joint pain from arthritis	bruises, strains/sprains
OTC	Rx only
4x/day for 21 days	1 patch BID
adults only	age 6+

Topical diclofenac

- Advantages:
  - decreased systemic absorption of NSAID compared to oral
  - less risk of GI, renal, & cardiovascular SE
- Side effects: local skin reactions (itching, burning, rash)
- Most effective on superficial joints
  - UE: hands, wrists, elbows
  - LE: knees, ankles, feet

Topical diclofenac

- Cochrane review: “about 60% of patients achieved **≥ 50% improvement in pain**…”

- UpToDate: “especially beneficial for **mild OA in the knee and hand**”

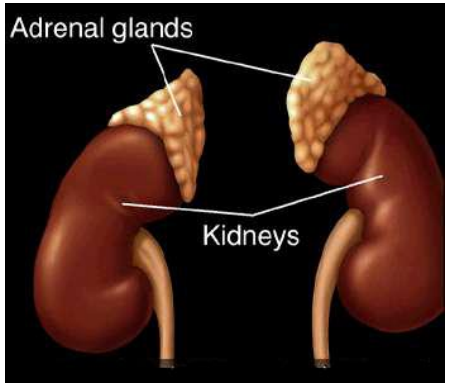
So…capsaicin or diclofenac??

- UpToDate: “we prefer topical NSAIDS over capsaicin…due to **better tolerability** and **stronger evidence for efficacy**”

Injections: **glucocorticoids**

Patients taking > 5mg/day of ***oral*** prednisone (or equivalent), have an increased risk of:

- osteoporosis
- Cushing's syndrome
- hypertension
- sleep disturbances
- avascular necrosis
- hypokalemia
- immunosuppression/infections
- hunger/weight gain
- cataracts
- hyperglycemia
- mood changes
- suppression of HPA axis



Injections: **glucocorticoids**

- Injections > Oral

- Glucocorticoids have potent anti-inflammatory capabilities
  - inhibit inflammatory leukocytes
  - inhibit prostaglandins & leukotrienes

Injections: **glucocorticoids**

Indications:

- anti-inflammatory
- analgesic (mild)

Common Uses:

- joint DJD
- bursitis
- ganglion cyst
- lateral epicondylitis/epicondylosis (tennis elbow)
- carpal tunnel syndrome
- trigger finger

- Differences: joint vs. tendon vs. bursa vs. tendon sheath

Injections: **glucocorticoids**

Intra-tendinous steroids cause:

- collagen necrosis
- decreased tensile strength

- Therefore considered a “last resort” conservative measure prior to surgery for UPPER EXTREMITY tendons only
  - Example: lateral epicondylitis/epicondylosis (tennis elbow)

- Never inject steroids into Achilles tendon or patellar tendon!

Injections: **glucocorticoids**

Bursal injections are considered safe:

- trochanteric bursitis (lateral hip)
- pes anserine bursitis (below the knee)
- sub-acromial bursitis (postero-lateral shoulder)

Tendon sheath injections are considered safe:

- trigger finger (stenosing tenosynovitis)
- ganglion cyst (“cyst” is from tear in the tendon sheath)

Injections: **glucocorticoids**

Intra-articular steroids:

Remain quite common clinically

UpToDate:

- "the use…for OA is falling out of favor as there is increasing evidence that serial injections have negative effects on the progression of cartilage damage in knee OA"
  - 2017 RCT: 140 patients with knee OA
  - triamcinolone
  - cartilage volume loss (by MRI)

Injections: **glucocorticoids**

Intra-articular steroids:

Practically:

- Intra-articular steroids are generally well tolerated
- Do provide good analgesia

- Yes, too many may harm articular cartilage…
  - using in population who already have articular cartilage degradation

Injections: **glucocorticoids**

Intra-articular steroids:

Potential Adverse Effects:

1. Septic arthritis
   - mitigate this by using proper sterile technique

2. Transient synovitis ("steroid flare")
   - More soluble → less duration → less chance of flare
   - Less soluble → longer duration → more chance of flare

3. Skin hypopigmentation/fat atrophy

Injections: **glucocorticoids**

Intra-articular steroids:

Note: sometimes necessary to reassure patients:

- glucocorticoid ≠ anabolic steroid

Therapeutic Goal:

- maximize anti-inflammatory effects
- minimize potential side effects

Injections: **glucocorticoids**

Steroid Solution	Potency	Half-life	Duration	Typical Dose/Volume
hydrocortisone (Cortisone)	low	8-12 hrs	short	50mg/mL
triamcinolone (Kenalog)	medium	12-36 hrs	medium	4mg/mL
methylprednisolone (Depo-Medrol)	medium	12-36 hrs	long	40mg/mL
dexamethasone (Decadron)	high	24-48 hrs	longer	8mg/mL

Injections: **glucocorticoids**

Intra-articular steroids:

Common Practice:

- very little risk if utilized sporadically
  - repeat every 3 months, as needed
  - (max of 4 intra-articular injections per year)

- benefits may wane after 2-years of therapy

Injections: **hyaluronic acid**

- polysaccharide
- chief component of extracellular matrix
  - tissue regeneration, inflammation, angiogenesis
- found in:
  1. articular cartilage
  2. fibroblasts
  3. skin
  4. synovial joint fluid

Injections: **hyaluronic acid**

- Utilized for:
  1. wound healing (burns, diabetic ulcers)
  2. dermal filler (facial wrinkles)
  3. osteoarthritis
     - joint injections
     - aka visco-supplementation

Injections: **hyaluronic acid**

Mechanism of action: not well understood

HA is normal component of joint fluid

- but decreased by 50% in DJD

Injections: **hyaluronic acid**

No chemical reaction taking place

HA is very thick, “takes up space”

- FDA approved as a ***medical device!***
- “viscous lubricant & shock absorber”

Injections: **hyaluronic acid**

Brands:

- Hyalgan
- BioVisc Ortho
- Supartz
- Orthovisc
- Gelsyn
- Synvisc
- Euflexxa

Injections: **hyaluronic acid**

UpToDate:

- "…longstanding debate and conflicting data across trials…regarding the benefit of visco-supplementation"

- small, but ***clinically irrelevant*** benefit over placebo

- high costs (not often covered by INS)

Injections: **hyaluronic acid**

Originally approved for knee OA:

- but used off-label for shoulder, ankle, wrist, hip, etc.

No consensus on:

- number of injections per dose (single, series of 3 or 5?)
- injection frequency (q 6-months, q 12-months?)
- optimal volume per dose

Typically used ***after*** corticosteroid has failed, but ***before*** joint replacement

Injections: **platelet rich plasma**

Alternate names:

- autologous platelet-derived growth factors (APDGF)
- autologous conditioned plasma (ACP)

Since 1970's has gained popularity in many fields:

- otolaryngology
- dentistry, maxillofacial surgery
- cosmetic surgery
- neurosurgery
- wound healing
- spine surgery
- veterinary medicine
- orthopedics

Injections: **platelet rich plasma**

Extraordinary interest within orthopedics perhaps due to ***high-profile athletes*** & associated media coverage

Advocates claim:

- decreased pain
- improved healing time
- less post-op opioid use
- stronger surgical repairs

Injections: **platelet rich plasma**

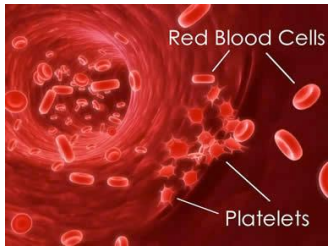
GOAL: to utilize a supra-physiological concentration of autologous growth factors to facilitate repair & restoration of injured tissue

Stimulate & enhance the healing process

- especially areas typically poor in blood supply (tendons/ligaments)

A “growth factor cocktail” to enhance and accelerate the body’s natural tissue healing ability *(Schwarz, 2009)*

Injections: **platelet rich plasma**



Platelets:

- essential role in primary hemostasis (forming the clot)
- also important to inflammatory response & therefore tissue healing

Platelets store/release growth factors from α-granules

Growth factors - proteins responsible for cell communication

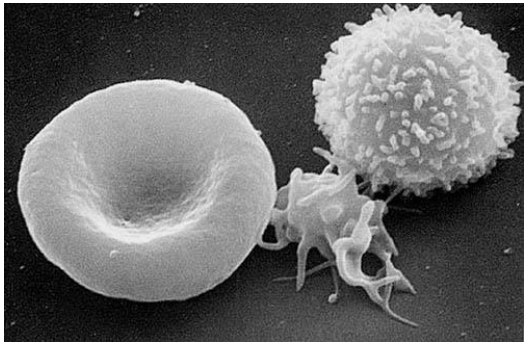
- act as cytokines (signaling molecules) between cells
- initiate cellular differentiation/growth/proliferation

Injections: **platelet rich plasma**

Growth factors known to be released by platelets:

- transforming growth factor beta (TGF-b)
- platelet-derived growth factor (PDGF)
- vascular endothelial growth factor (VEGF)
- insulin-like growth factor (IGF)
- fibroblast growth factor-2 (FGF-2)
- platelet-derived endothelial growth factor (PDEGF)
- epidermal growth factor (EGF)

(Alsousou, 2009)

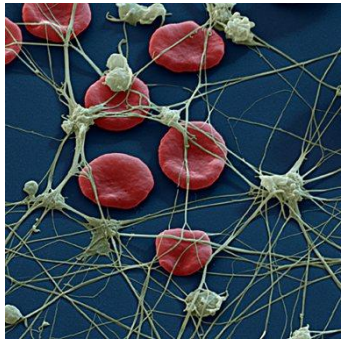


Injections: **platelet rich plasma**

Normal platelet counts in blood: 150,000 – 350,00/µl

PRP working definition: ≥ 1 million platelets/µL *(Marx, 2001)*

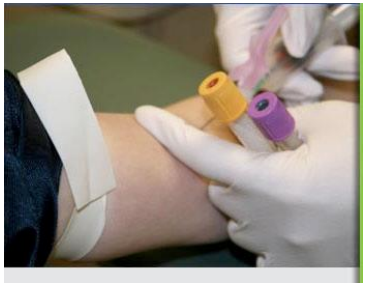
Alternative definition: 3-5x increase growth factor concentrations *(Foster, 2009)*



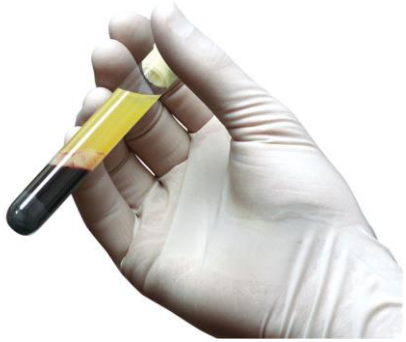
Injections: **platelet rich plasma**

How is PRP therapy done?

Step 1: Venipuncture *(amount needed depends on system)*

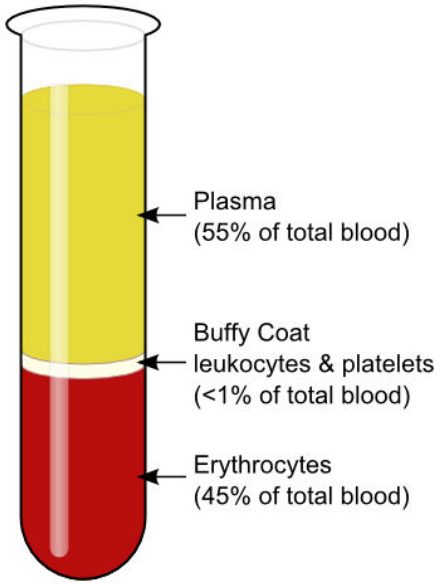


Step 2: Centrifugation



Injections: **platelet rich plasma**

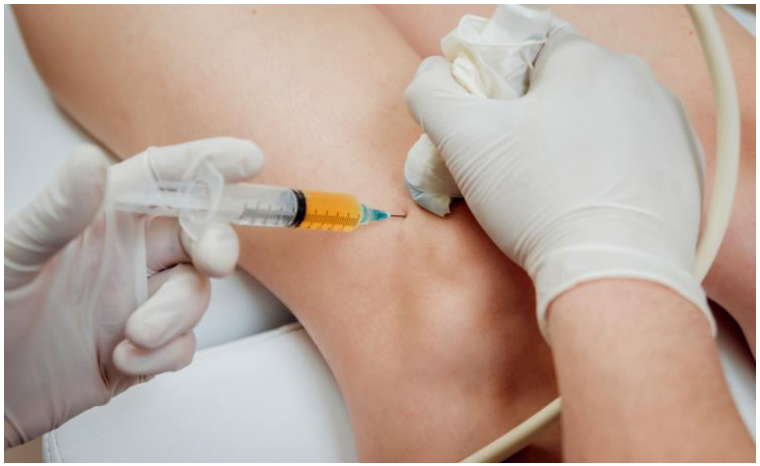
How is PRP therapy done?

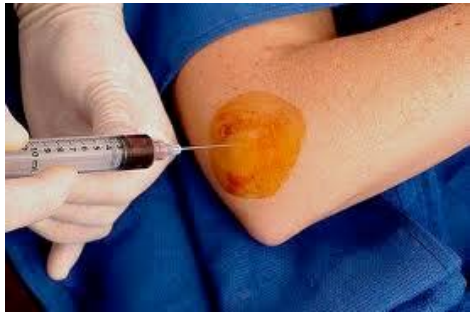


Injections: **platelet rich plasma**

Step 3: Inject at site of injury

- If available, use ultrasound guidance (recommended)





Injections: **platelet rich plasma**

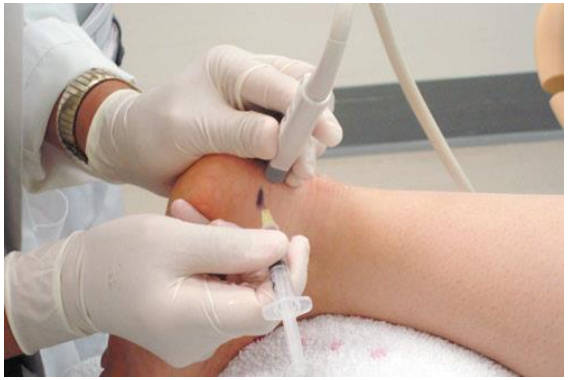
Step 4: Post-injection care

- No NSAIDS
- Rest the extremity
  - UE: sling or brace
  - LE: crutches or walking boot
- Therapeutic exercise?

Injections: **platelet rich plasma**

Purported **Clinical** Uses

- Shoulder – biceps tendonopathy
- Hip – hamstring strain, trochanteric bursitis
- Elbow – medial or lateral epicondylitis
- Knee – patellar tendonitis, quad strains, MCL sprains
- Ankle – Achilles tendonitis
- Foot – plantar fasciitis

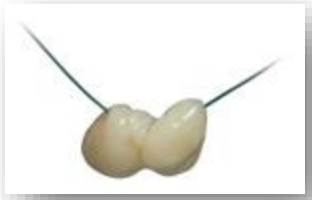


Injections: **platelet rich plasma**

Purported **Surgical** Uses

To ***augment*** surgical repairs & reconstructions:

- Shoulder
  - rotator cuff repair
- Knee
  - meniscus repair
  - ACL reconstruction
  - bone tunnel healing
- Ankle
  - Achilles tendon repairs



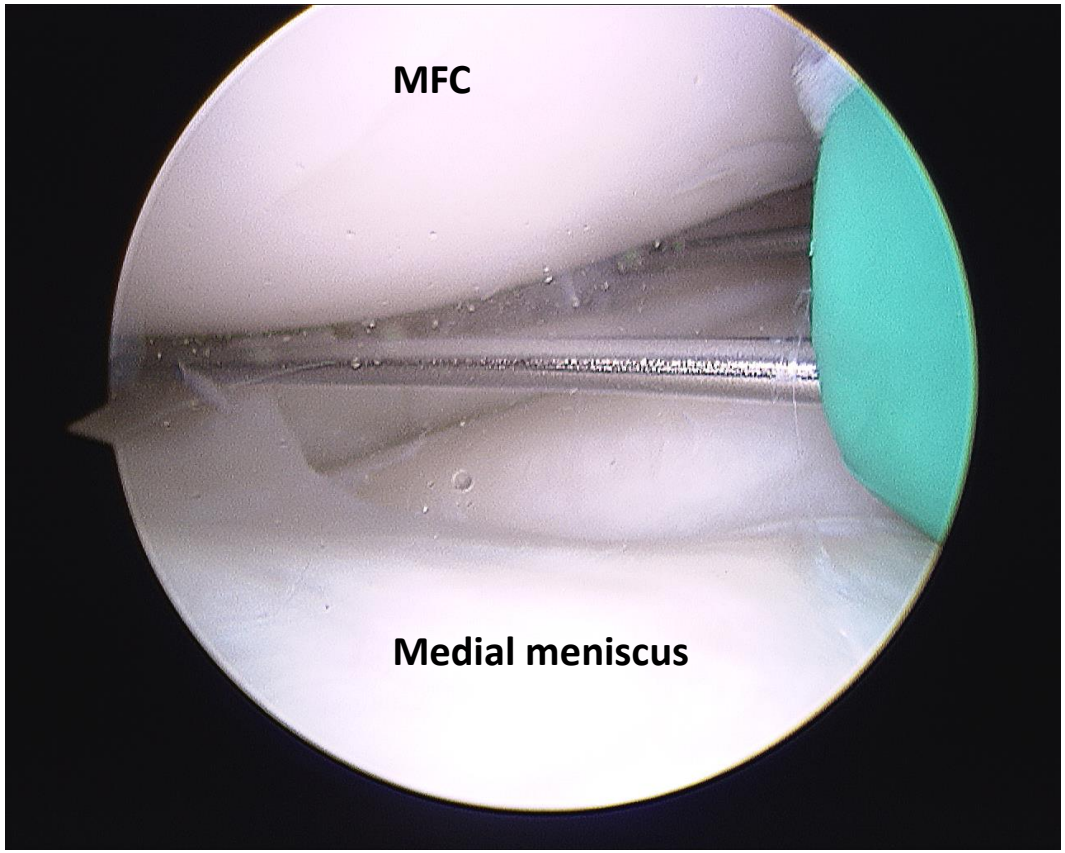
Injections: **platelet rich plasma**

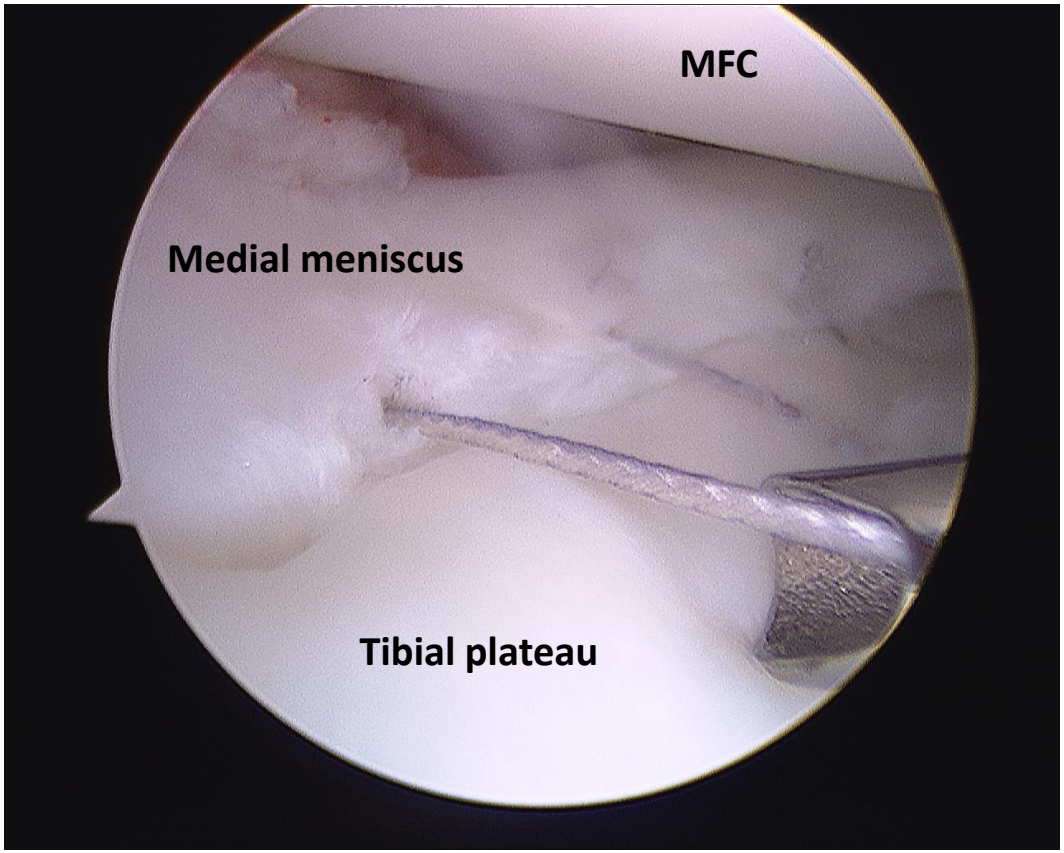
Purported **Surgical** Uses

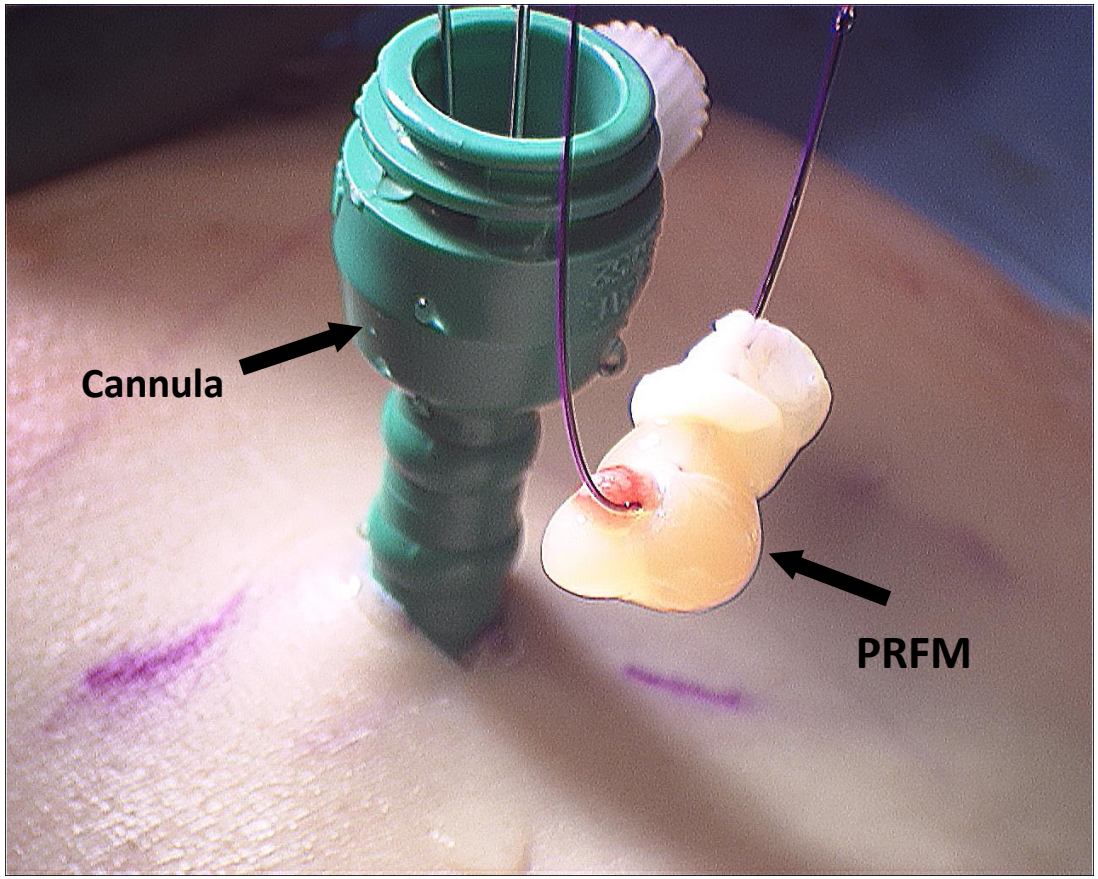
Initial steps are the same (blood draw, centrifuge, PRP from top)

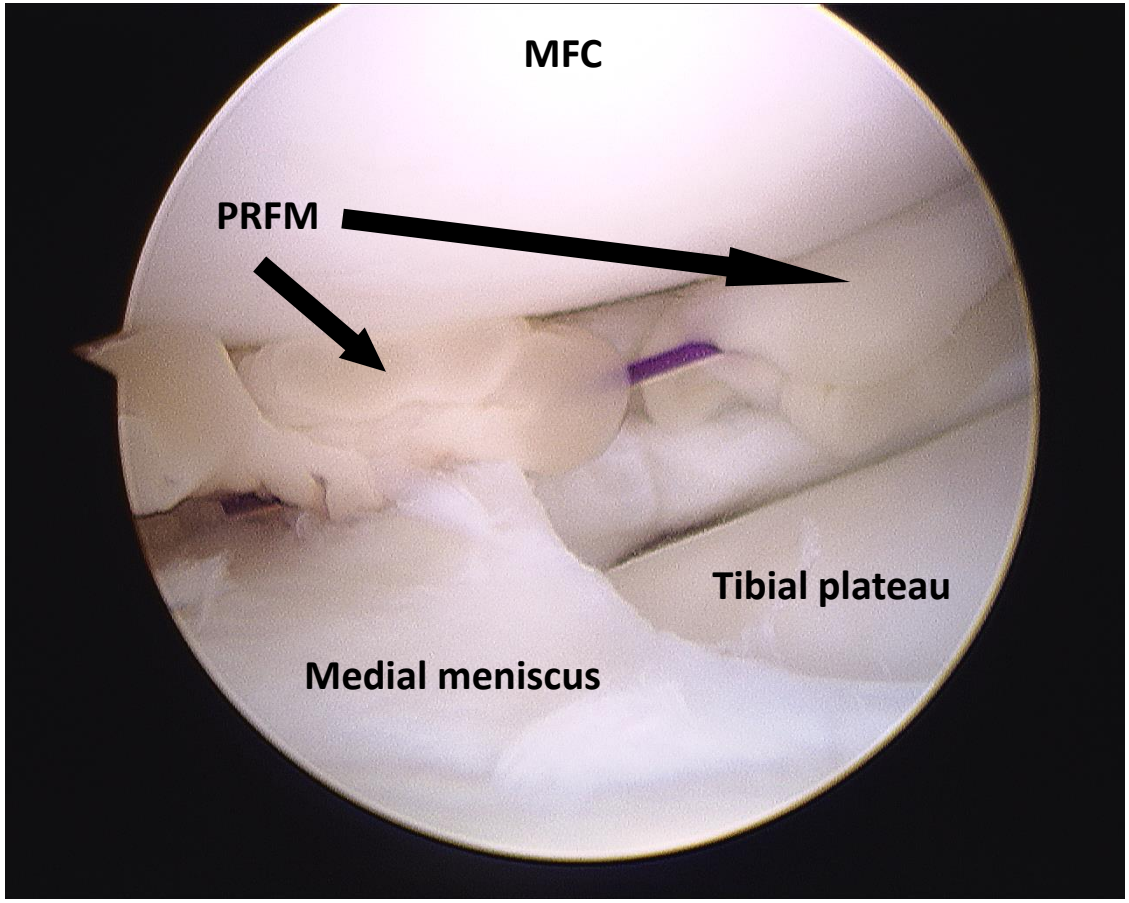
…then PRP is mixed with activating agent, 2nd centrifuge cycle

This creates a “platelet rich fibrin matrix” (PRFM)


MFC
Medial meniscus


MFC
Medial meniscus
Tibial plateau


Cannula
PRFM


MFC
PRFM
Tibial plateau
Medial meniscus

Injections: **platelet rich plasma**

What's the ***evidence***?

Injections: **platelet rich plasma**

2004 - Barret & Erredge

Plantar fasciitis

Dx confirmed by ultrasound
PRP injection to medial band of plantar fascia

66% of pts w/ complete relief at 2 months
78% at 1 year

Injections: **platelet rich plasma**

2005 - Cuget, et al

Acute muscle injuries (direct mechanical trauma)

14 Pro athletes w/ 16 muscle injuries

PRP injected under U/S guidance after hematoma aspiration

>50% reduction in RTP time (in less severe injuries only)

Injections: **platelet rich plasma**

2006 - Mishra & Pavelko

Lateral epicondylitis

Tx group: 15 pts received PRP
Control group: 5 pts received local anesthetic

	8 weeks	6 months	2 years
Tx group (VAS)	60% improve	81% improve	93% improve
Control (VAS)	16% improve	N/A	N/A

Tx group also reported:

- 93% satisfaction
- 94% return to work/sport
- 99% return to ADLs

Injections: **platelet rich plasma**

2008 - Kajikawa, et al

Patellar tendonitis – Histologic study

- injected PRP into patellar tendon of rats

Tissue analysis:

- increased levels of Type I collagen & macrophages brought to injured area
- “consistent with repair/remodeling of tendon”

Injections: **platelet rich plasma**

2009 - Kon, et al

Chronic patellar tendonitis

- 20 male athletes each w/ 3 PRP injections at 15-day intervals

80% of pts were “satisfied”
70% showed “complete or marked recovery”

Injections: **platelet rich plasma**

2009 - Mandelbaum & Gerhardt

Acute MCL sprains in Pro soccer players

Tx group: single PRP injection w/in 72 hours of injury
Control group: rest and rehab

RTP time was lessened by 27% compared to control group

Injections: **platelet rich plasma**

2010 - de Vos, et al

Chronic Achilles tendonopathy

Tx group: 27 pts – PRP injection w/ ultrasound guidance
Control group: 27 pts – placebo (saline injection)

At 6-month follow-up:

- No difference in pain scores or functional measures
- Both groups with similar (57%) return-to-sport rate

Injections: **platelet rich plasma**

2011 - Castricini, et al

Arthroscopic Rotator Cuff Repair

88 patients total, w/ small-to-medium sized tears

- 45: standard repair
- 43: standard repair w/ PRP augmentation

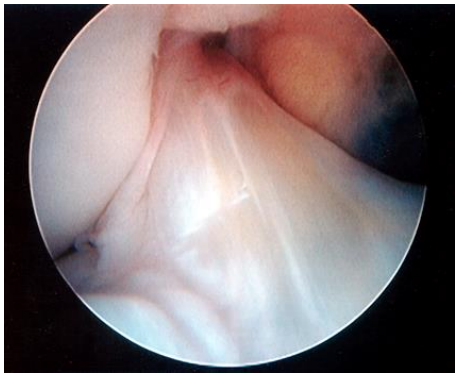
At average follow-up of 20.2 months:

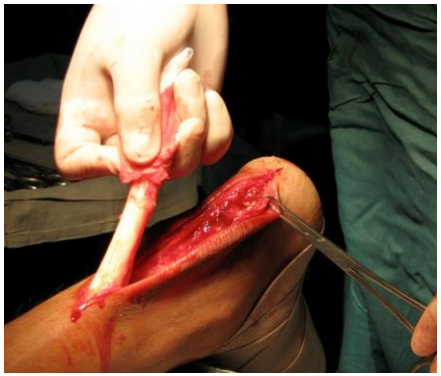
- No significant improvement in shoulder function
- No significant improvement in structural outcome

Injections: **platelet rich plasma**

SUMMARY

- Too much ***heterogeneity*** in the literature
- Minimal Level 1 evidence





Injections: **platelet rich plasma**

SUMMARY

- Safe (autologous)
- Not standard of care
  - not typically reimbursed by INS

Injections: **platelet rich plasma**

Orthopedics typically focuses on ***mechanical*** and ***structural*** repair of joints/bones…

…PRP therapy is part of the expanding field of ***"orthobiologics"***:

- synthetic bone graft
- cartilage repair
- allograft tissue
- stem cell therapy, and more!

Outline

Oral Agents

- glucosamine/chondroitin
- seratonin/norepinephrine re-uptake inhibitors (SNRIs)
- muscle relaxants

Topicals

- lidocaine
- capsaicin
- diclofenac

Injections

- glucocorticoids
- hyaluronic acid
- platelet rich plasma