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)
- skeletal muscle relaxants

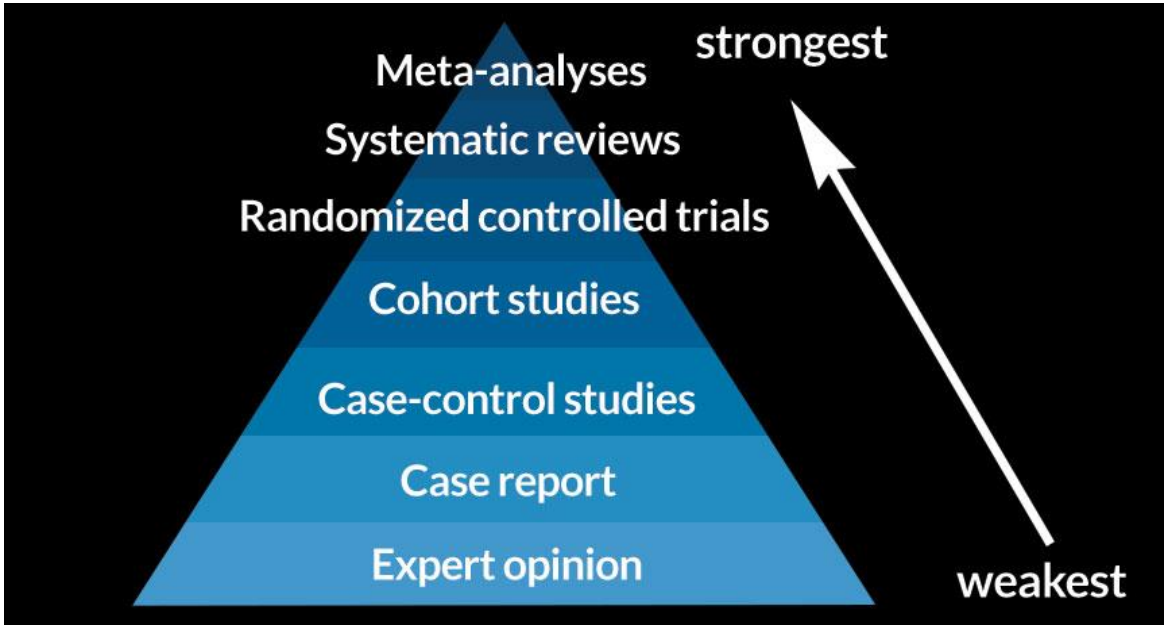
Topicals

- lidocaine
- capsaicin
- diclofenac

Injections

- glucocorticoids
- hyaluronic acid
- platelet rich plasma

Evidence-based??



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

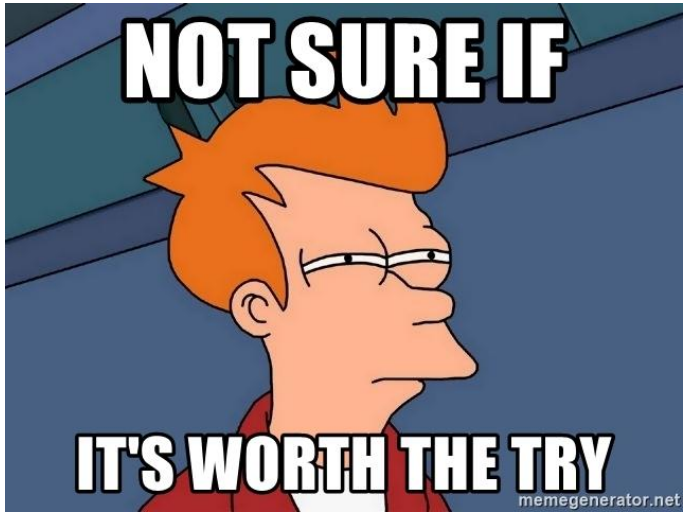
Glucosamine & Chondroitin

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

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

Glucosamine & Chondroitin

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



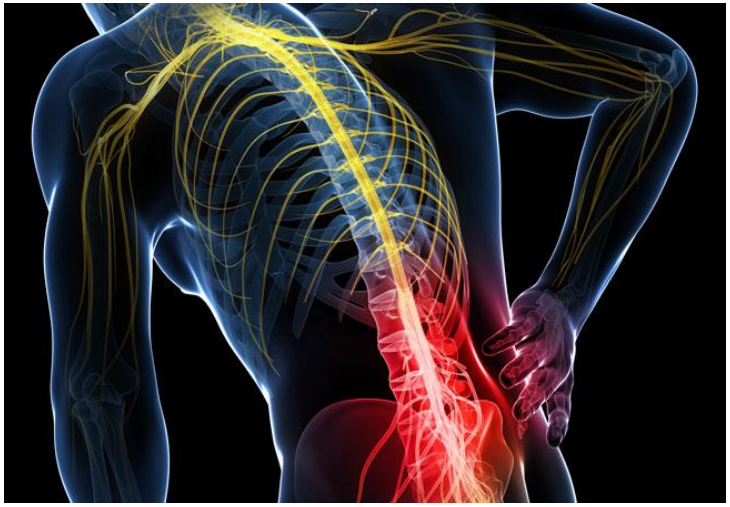
SNRIs

- 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

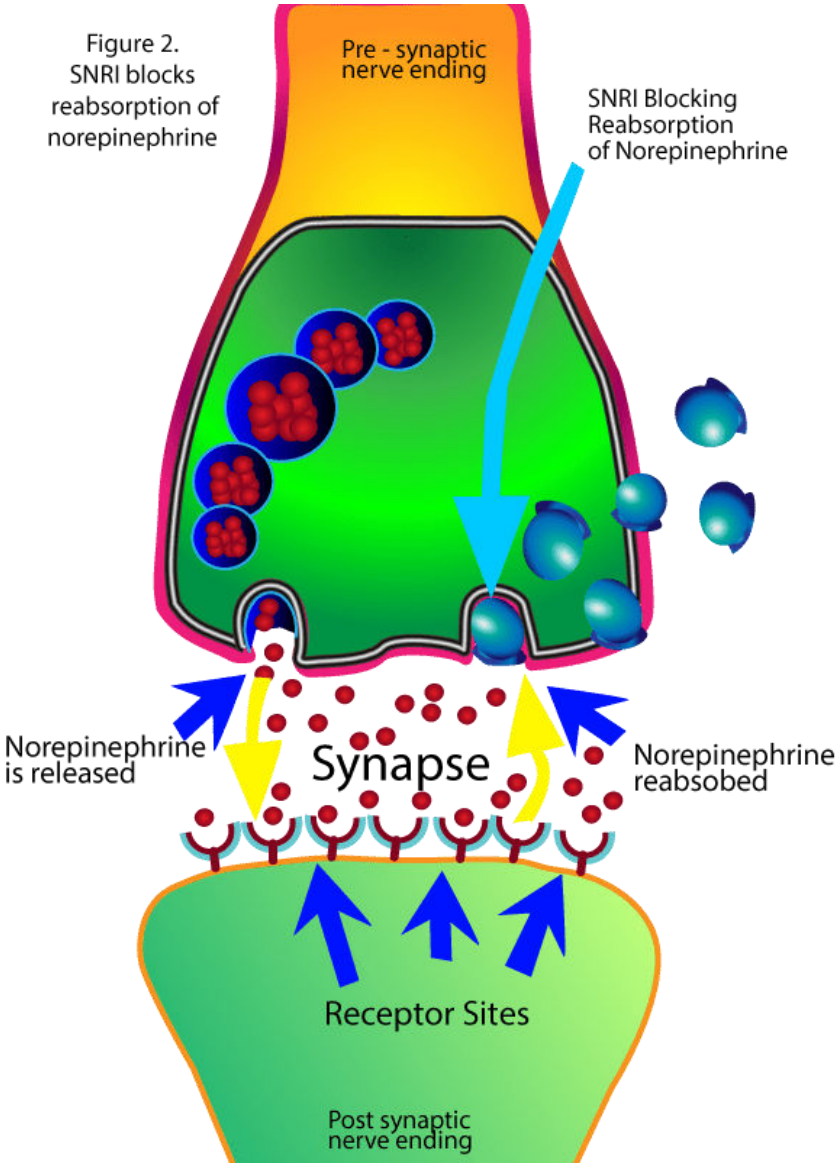
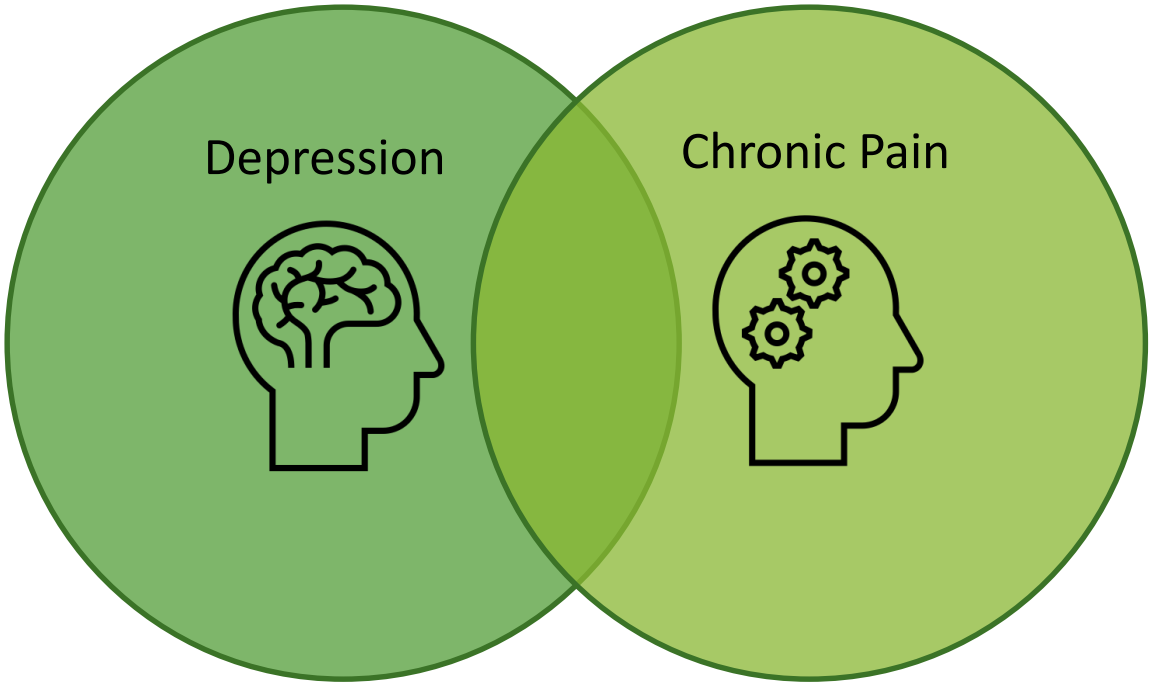


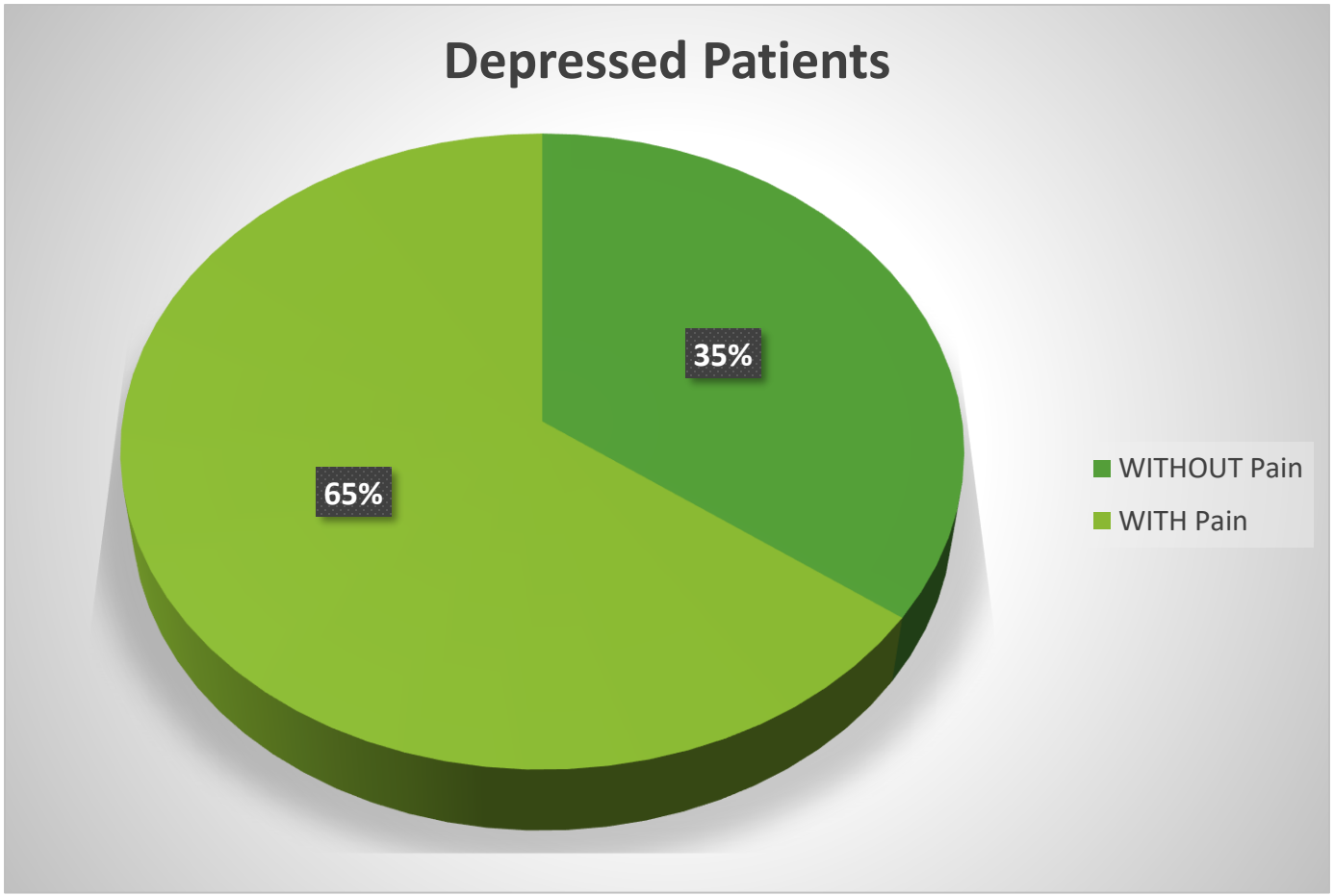
Figure 2.
SNRI blocks
reabsorption of
norepinephrine
Pre - synaptic
nerve ending
SNRI Blocking
Reabsorption
of Norepinephrine
Norepinephrine
is released
Synapse
Norepinephrine
reabsobed
Receptor Sites
Post synaptic
nerve ending

SNRIs



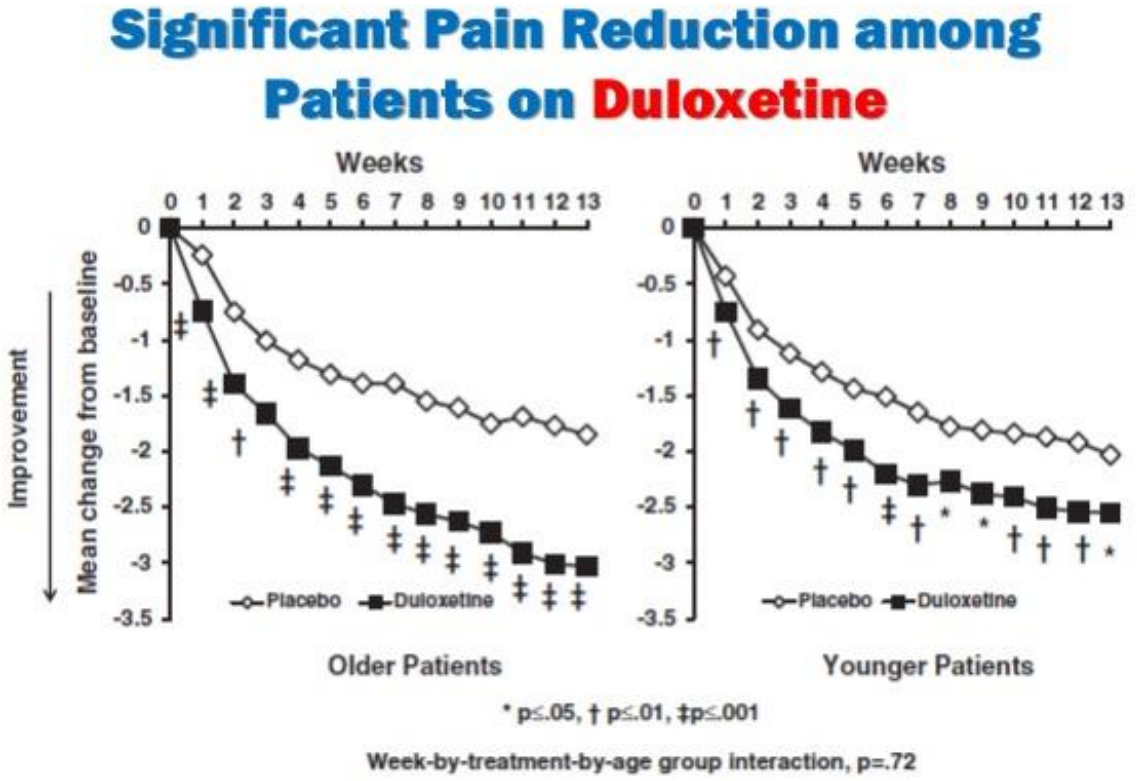
Shared Neurobiology/Neuroanatomy

SNRIs



Mean prevalence data from 14 studies

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

Skeletal Muscle Relaxants

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

Skeletal Muscle Relaxants

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

…no evidence that ‘muscle relaxants’ directly relax muscles

Skeletal 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)
  - a benzodiazepine such as diazepam (Valium)

Skeletal Muscle Relaxants

- Precise relationship between MSK pain & spasm is not well understood!
  - pain -> spasm -> more pain??

  - Painful muscles typically ***do not*** show EMG activity, and even when they do – the timing/intensity does not correlate with the pain

Skeletal Muscle Relaxants

Important Caveat:

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

Skeletal 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**

Skeletal Muscle Relaxants

Summary of Recommendations

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

Skeletal Muscle Relaxants

April 2022

- double blind, placebo-controlled study
- new onset, non-radicular, non-traumatic LBP
- 887 patients

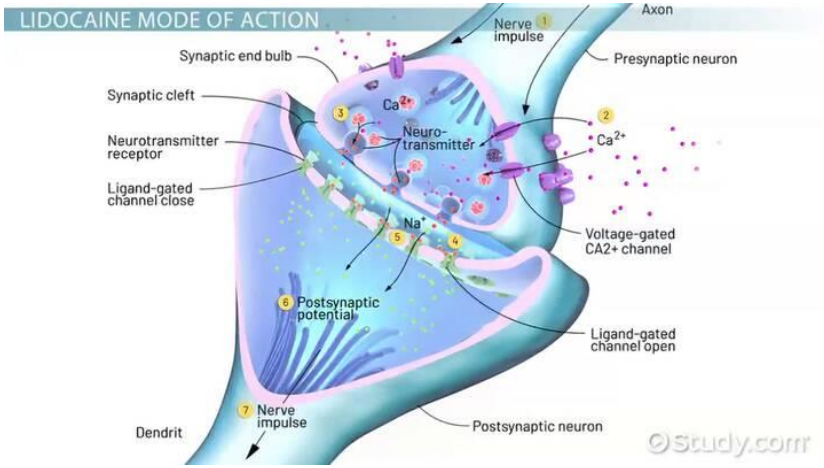
- All received naproxen, plus…
- Seven SMR's (baclofen, tizanidine, metaxalone, diazepam, orphenadrine, methocarbamol, cyclobenzaprine)

Skeletal 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

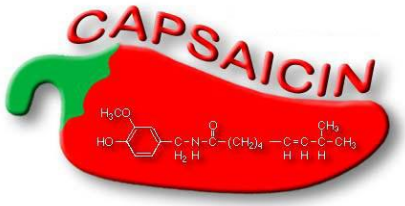
Topical lidocaine

- Widely used in current practice because:
  - limited systemic absorption
  - relative lack of systemic side effects

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

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**”

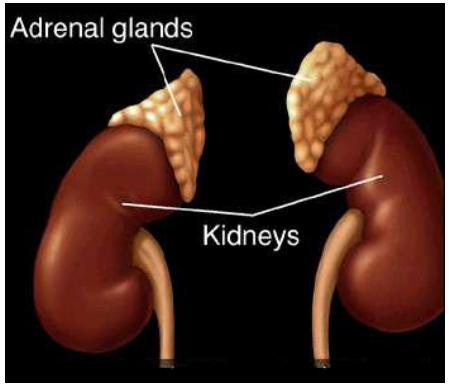
So…capsaicin or diclofenac??

- 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**

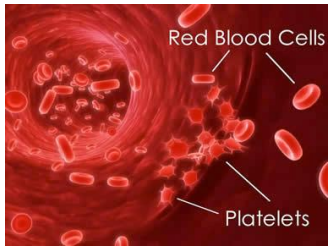
GOAL: to utilize a supra-physiological concentration of autologous growth factors to facilitate repair & restoration of injured tissue

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

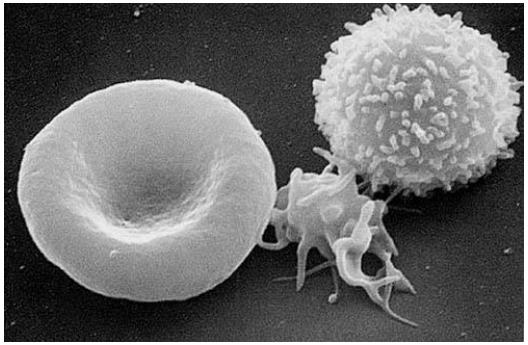
- act as cytokines (signaling molecules) between cells
- initiate cellular differentiation/growth/proliferation

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)

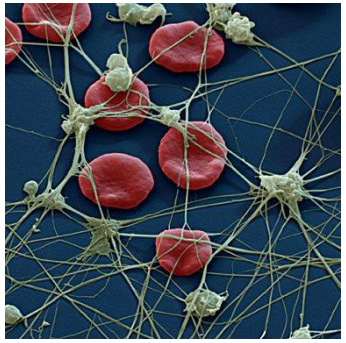


Injections: **platelet rich plasma**

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

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

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

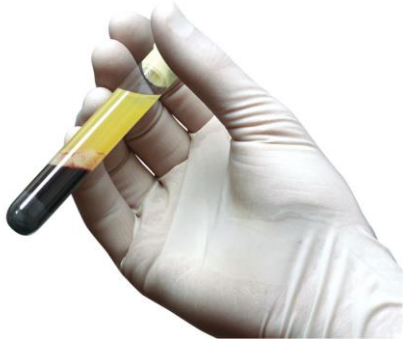


Injections: **platelet rich plasma**

How is PRP therapy done?

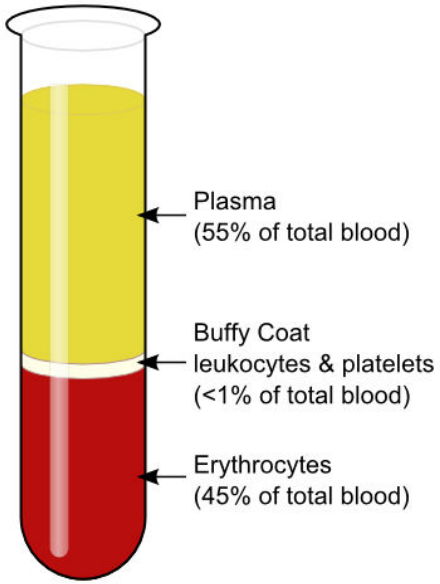
Step 1: Venipuncture *(amount needed depends on system)*

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

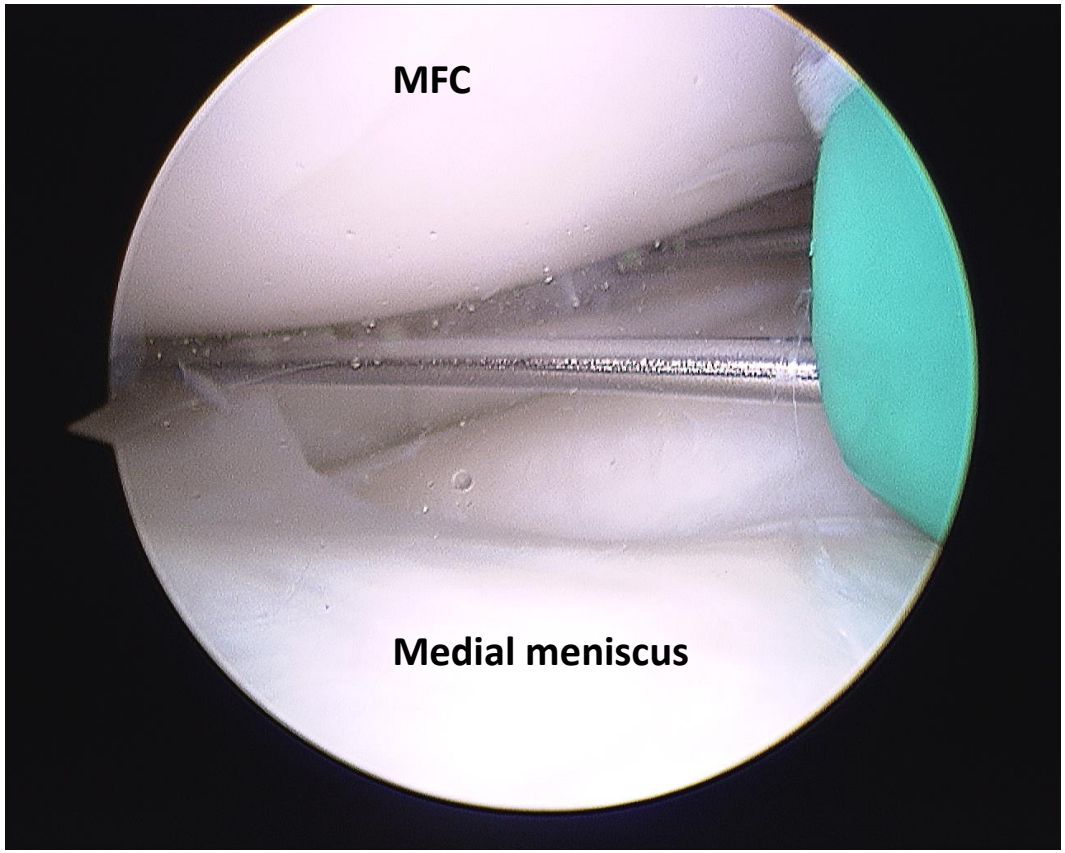
Injections: **platelet rich plasma**

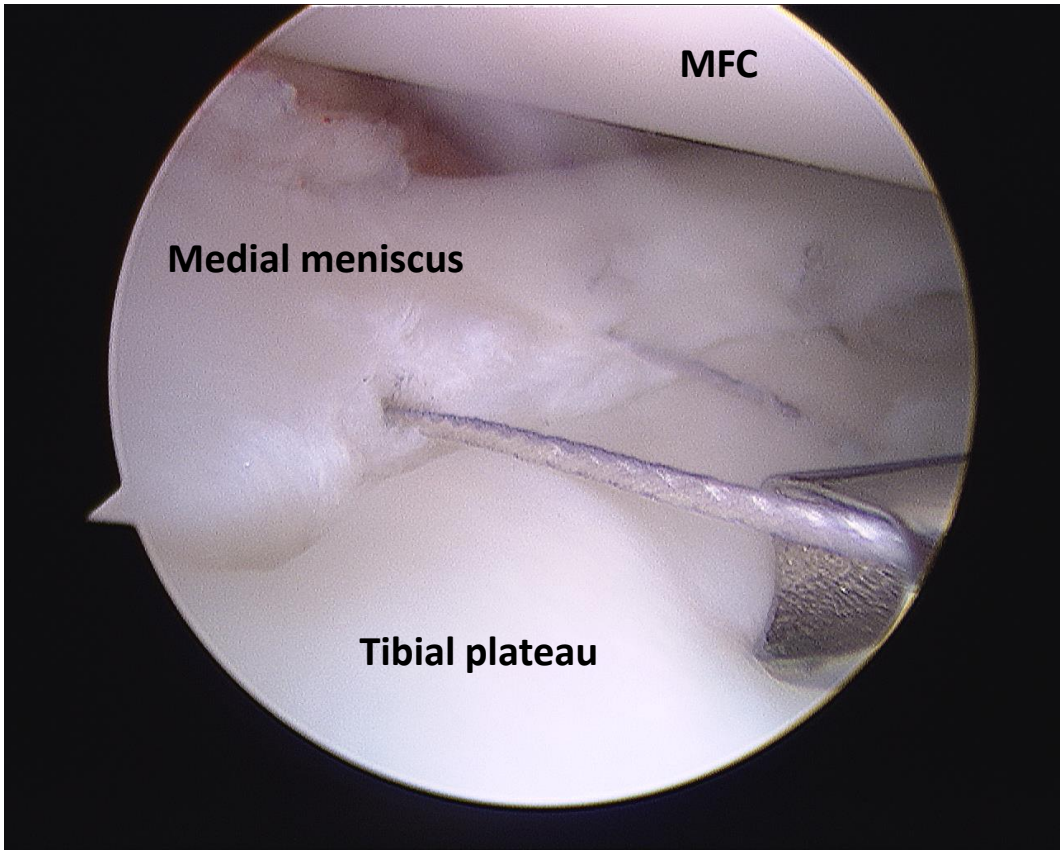
Purported **Surgical** Uses

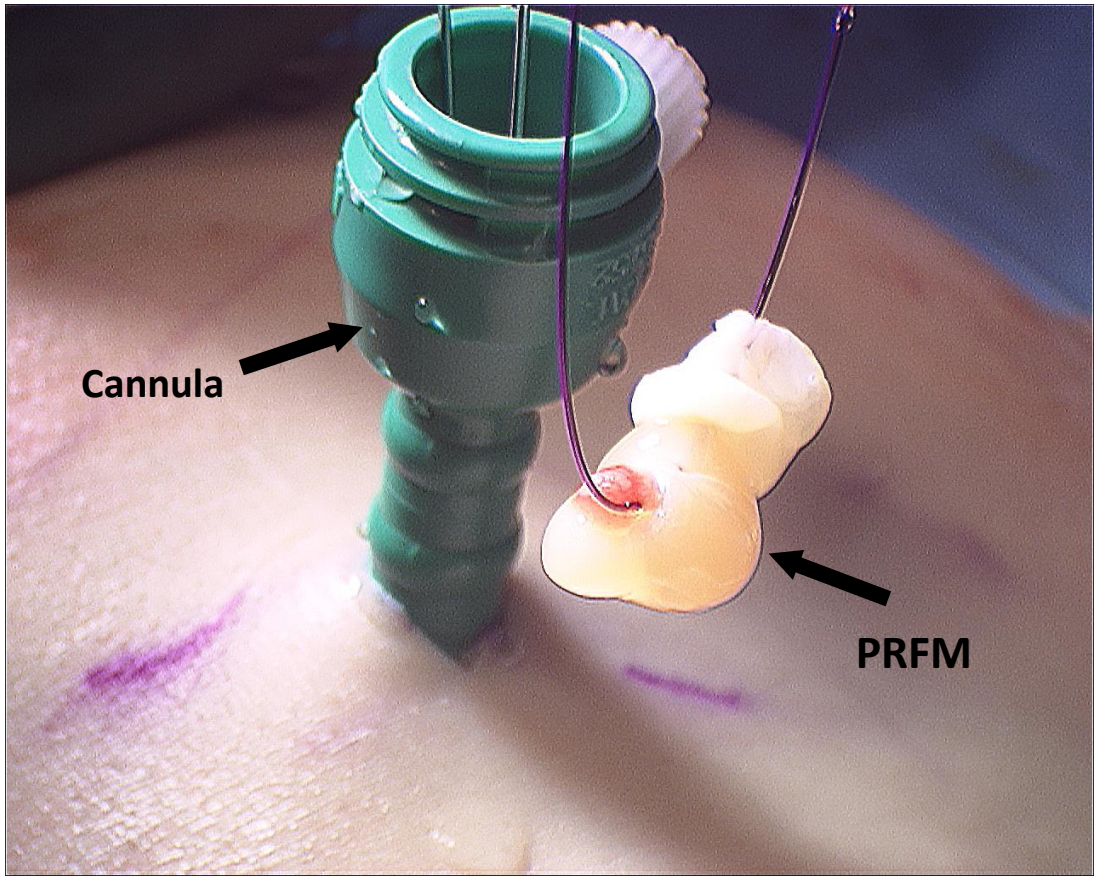
Initial steps are the same (blood draw, centrifuge, PRP from top)

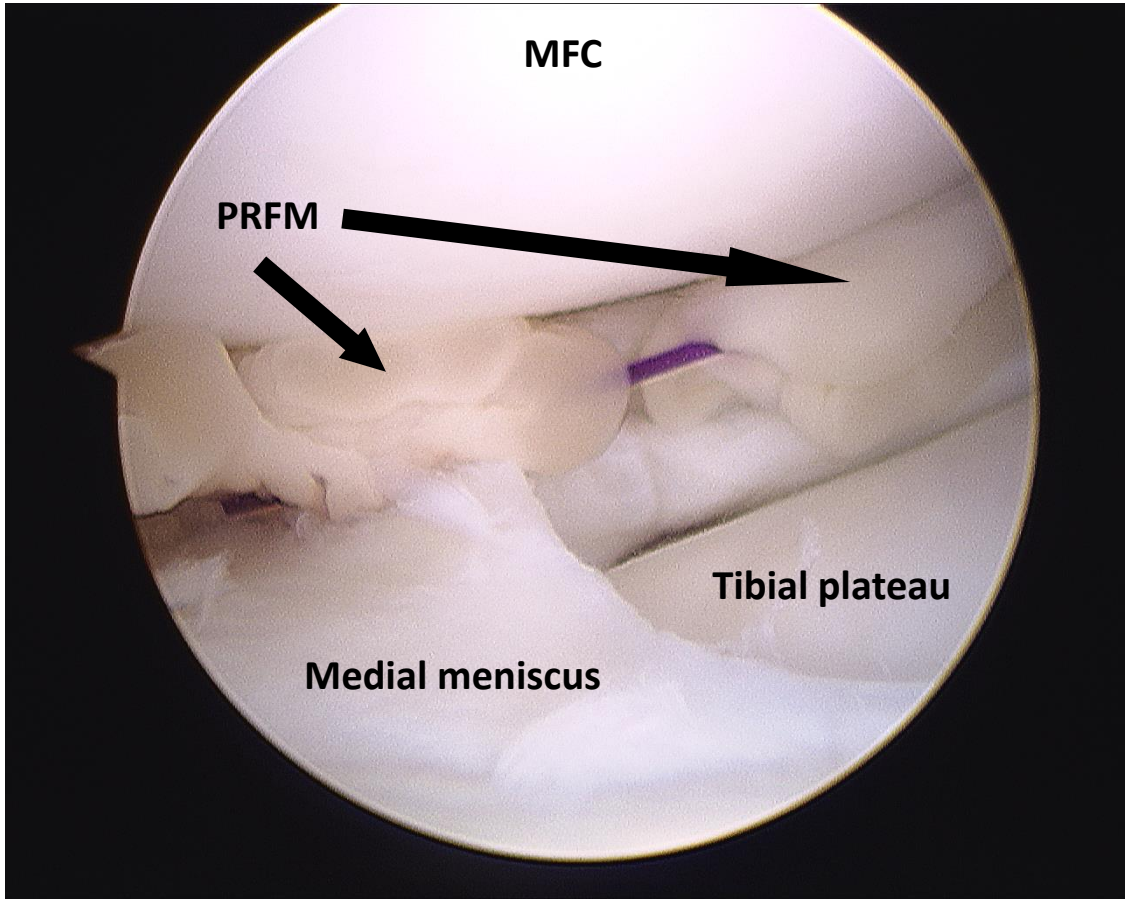
…then PRP is mixed with activating agent, 2nd centrifuge cycle

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**

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**

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**

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**

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**

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**

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**

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)
- skeletal muscle relaxants

Topicals

- lidocaine
- capsaicin
- diclofenac

Injections

- glucocorticoids
- hyaluronic acid
- platelet rich plasma