Gout and Osteoarthritis: What Works and What Doesn’t?

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Disclosures

None
Objectives
Osteoarthritis
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>🎃</td>
<td>OA affects ~30 million Americans (~35% of Americans ≥65yo)¹</td>
</tr>
<tr>
<td>🧑‍🤝‍🧑</td>
<td>A leading cause of disability among older adults in the US, top 10 causes of disability worldwide¹</td>
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<td>💰</td>
<td>5th most expensive condition treated in US hospitals @ $40 billion¹</td>
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<tr>
<td>$</td>
<td>Annual direct per-patient cost $1500 - $20,000²</td>
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<td>👮‍♀️</td>
<td>~25% of OA patients have limitations in activities of daily living¹</td>
</tr>
<tr>
<td>🔴</td>
<td>Increased CVD risk, depression, suicidal ideation²</td>
</tr>
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</table>

1 Osteoarthritis and Cartilage 21 (2013) 1145-1153
2 Curr Opin Rheumatol. 2018 March; 30(2): 160-167

**Osteoarthritis Highlights**
Clinical Features Osteoarthritis

- Worse with activity
- Morning stiffness < 30 minutes
- “Gelling”
- Bony hypertrophy
- Limited mobility
- Crepitus
Heberden’s and Bouchard’s nodes signify primary nodal OA
Pathophysiology
Osteoarthritis

Articular Cartilage

Trauma/Microfracture

Chondrocyte transformation to inflammatory catabolic phenotype

Degradation of ECM (metalloproteinases)

Macrophage Activity/Cytokine Release

Subchondral bone exposure
Exposed to synovial fluid + growth factors

Rapid attempt to refortify

Hypomineralized bone

Suboptimal shock absorption

Subchondral Bone
## Table 2. Inflammatory mediators in osteoarthritis.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Chemokines</th>
<th>Growth factors</th>
<th>Adipokines</th>
<th>Prostaglandins/leukotrienes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα [Saklatvala, 1986]</td>
<td>RANTES [Hsu et al. 2004]</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

IL, interleukin; LTB4, leukotriene B4; MCP, monocyte chemotactic protein; MIP-1, macrophage inflammatory protein; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.
What Works for Osteoarthritis?
Treatment for OA

- Nonpharmacologic
  - Patient Education, Low-impact Exercise, PT, Aqua PT, Weight loss
- Drugs (Tylenol, NSAIDs, Tramadol, Opioids)
- Supplements (+/- glucosamine + chondroitin sulfate, curcumin)
- Injections (CSI, HAI)
- Clinical Trials (DMOADs)
Education on disease, treatment and recommendations → improved pain and function long term

Major obstacle is *quality of education* given by healthcare providers

Multidisciplinary approach is generally beneficial for patient outcomes (physician, nurse, pharmacist, physical therapist)
<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical therapy using land-based or water-based exercise can help reduce pain and</td>
<td>B</td>
<td>10-12</td>
</tr>
<tr>
<td>improve function in patients with osteoarthritis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen should be used as first-line therapy for mild osteoarthritis.</td>
<td>A</td>
<td>16</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs are superior to acetaminophen for treating</td>
<td>A</td>
<td>16</td>
</tr>
<tr>
<td>moderate to severe osteoarthritis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-articular corticosteroid injections can be beneficial for short-term (i.e.,</td>
<td>A</td>
<td>21, 22</td>
</tr>
<tr>
<td>less than eight weeks) relief of osteoarthritis pain of the knee.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared with intra-articular corticosteroids, intra-articular hyaluronic acid</td>
<td>B</td>
<td>26, 27</td>
</tr>
<tr>
<td>injections of the knee are less effective in the short term, equivalent in the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intermediate term (i.e., four to eight weeks), and superior in the long term.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The combination of glucosamine and chondroitin may decrease pain in patients with</td>
<td>B</td>
<td>30</td>
</tr>
<tr>
<td>moderate to severe knee osteoarthritis, although the evidence for this effect is</td>
<td></td>
<td></td>
</tr>
<tr>
<td>limited and inconsistent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who have continued pain and disability from osteoarthritis of the hip, knee,</td>
<td>B</td>
<td>35</td>
</tr>
<tr>
<td>or shoulder despite maximal medical therapy are candidates for total joint replacement.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.*
<table>
<thead>
<tr>
<th>Table 3. Nonpharmacologic recommendations for the management of knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>We strongly recommend that patients with knee OA should do the following:</td>
</tr>
<tr>
<td>Participate in cardiovascular (aerobic) and/or resistance land-based exercise</td>
</tr>
<tr>
<td>Participate in aquatic exercise</td>
</tr>
<tr>
<td>Lose weight (for persons who are overweight)</td>
</tr>
<tr>
<td>We conditionally recommend that patients with knee OA should do the following:</td>
</tr>
<tr>
<td>Participate in self-management programs</td>
</tr>
<tr>
<td>Receive manual therapy in combination with supervised exercise</td>
</tr>
<tr>
<td>Receive psychosocial interventions</td>
</tr>
<tr>
<td>Use medially directed patellar taping</td>
</tr>
<tr>
<td>Wear medially wedged insoles if they have lateral compartment OA</td>
</tr>
<tr>
<td>Wear laterally wedged subtalar strapped insoles if they have medial compartment OA</td>
</tr>
<tr>
<td>Be instructed in the use of thermal agents</td>
</tr>
<tr>
<td>Receive walking aids, as needed</td>
</tr>
<tr>
<td>Participate in tai chi programs</td>
</tr>
<tr>
<td>Be treated with traditional Chinese acupuncture*</td>
</tr>
<tr>
<td>Be instructed in the use of transcutaneous electrical stimulation*</td>
</tr>
<tr>
<td>We have no recommendations regarding the following:</td>
</tr>
<tr>
<td>Participation in balance exercises, either alone or in combination with strengthening exercises</td>
</tr>
<tr>
<td>Wearing laterally wedged insoles</td>
</tr>
<tr>
<td>Receiving manual therapy alone</td>
</tr>
<tr>
<td>Wearing knee braces</td>
</tr>
<tr>
<td>Using laterally directed patellar taping</td>
</tr>
</tbody>
</table>
Exercise Prescription for Older Adults With Osteoarthritis Pain: Consensus Practice Recommendations
A Supplement to the AGS Clinical Practice Guidelines on the Management of Chronic Pain in Older Adults
American Geriatrics Society Panel on Exercise and Osteoarthritis

**TABLE 4 Guidelines for exercise for older adults with OA**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Intensity</th>
<th>Volume</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility: static stretch</td>
<td>Stretch to subjective sensation of resistance</td>
<td>1 stretch per key muscle group; hold position for 5–15 s</td>
<td>Once per day</td>
</tr>
<tr>
<td>Flexibility: longer term</td>
<td>Stretch to full range of motion</td>
<td>3–5 stretches per key muscle group; hold position for 20–30 s</td>
<td>3–5 times per week</td>
</tr>
<tr>
<td>Strength: resistance, isometric</td>
<td>Low–moderate: 40–60% MVC</td>
<td>1–10 submaximal contractions involving key muscle group; hold contraction for 1–6 s</td>
<td>Once per day</td>
</tr>
<tr>
<td></td>
<td>Low: 40% 1RM</td>
<td>10–15 repetitions</td>
<td>2–3 times per week</td>
</tr>
<tr>
<td></td>
<td>Moderate: 40–60% 1RM</td>
<td>8–10 repetitions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: &gt;60% 1RM</td>
<td>6–8 repetitions</td>
<td></td>
</tr>
<tr>
<td>Isotonic</td>
<td>Low–moderate: 40–60% of VO₂max/HRmax</td>
<td>Accumulation of 20–30 minutes</td>
<td>3–5 times per week</td>
</tr>
</tbody>
</table>

HRₘax, age-predicted heart rate maximum (based on 220 – age); 1RM, one repetition maximum (a measure of isotonic or dynamic strength); MVC, maximal voluntary contraction (a subjective measure of isometric strength); VO₂ₘax, maximal aerobic capacity (the maximum rate at which oxygen can be utilised by exercising muscle, a measure of aerobic fitness).
Table 4. Pharmacologic recommendations for the initial management of knee OA*

We conditionally recommend that patients with knee OA should use one of the following:
- Acetaminophen
- Oral NSAIDs
- Topical NSAIDs
- Tramadol
- Intraarticular corticosteroid injections

We conditionally recommend that patients with knee OA should not use the following:
- Chondroitin sulfate
- Glucosamine
- Topical capsaicin

We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics
Glucosamine/Chondroitin Sulfate

- Theory: Glucosamine is component of extracellular matrix
- In vitro studies: glucosamine increases synthesis of proteoglycans by chondrocytes
- Conflicting evidence
- Relief should be noted in 2-3 months, otherwise discontinue

Intra-Articular Tx

Corticosteroids:
- Q3-4 months
- Short-term efficacy demonstrated

Viscosupplementation
- Q6-12 months
- Shows some superior benefit for long-term efficacy

ACR 2012 Guidelines for OA Treatment
Action Plan

It’s important to establish an action plan with your patient.

Patients oftentimes just want to know their options and how to use them.
Tanezumab: anti-NGF monoclonal Ab – SC/IV
Tissue Gene-C: TGF-Beta 1 Transduced Chondrocytes – IA
SM04690: WNT pathway inhibitor – IA

DMOADs – Phase III Trials
• Anti-Nerve Growth Factor monoclonal antibody – IV/SC Q8 weeks
• Improved knee pain, stiffness, and limitations of physical function
• SE: abnormal peripheral sensation, rapid progression of OA with NSAID use
Safety and efficacy of subcutaneous tanezumab in patients with knee or hip osteoarthritis
Safety and efficacy of subcutaneous tanezumab in patients with knee or hip osteoarthritis
IL-1β elevates NGF expression in the synovium and chondrocytes

TGF-β1 induces NGF expression in the synovium and chondrocytes

Mechanical loading stimulates NGF expression by chondrocytes

Role of Nerve Growth Factor (NGF)
Tissue Gene-C (Invossa)
• High quantities of TGF-β1 in articular cartilage
• Overexpression of TGF-β1 → chondrogenesis and growth of articular chondrocytes
SM04690

- WNT pathway inhibitor – IA
- Dual MOA: anti-inflammatory and reduces cartilage degradation
- Clinically significant improvement in joint space width by x-ray

Gout
Gout Highlights

- Prevalence increasing worldwide
  ~2% in men > 30yo, women > 50yo
  ~9% in men > 80yo

- Most prevalent inflammatory arthritis in men > 40yo

- Positive Family History in 25%

- Risk Factors: diet, obesity, metabolic syndrome, HTN, diuretics, CKD, ARBs, β-blockers

- Protective: low-fat dairy, coffee, vitamin C, CCB, losartan
<table>
<thead>
<tr>
<th>Monoarticular (85%)</th>
<th>Abrupt, Rapid (hours)</th>
<th>Night or Early morning</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- Low-grade fever</td>
<td>Articular and Extra-articular</td>
<td>Acral distribution</td>
</tr>
</tbody>
</table>
Gout Pathophysiology

- **Urate underexcretion (90%)**
  - Impaired renal urate transport
  - Hyperparathyroidism, hypothyroidism
  - Metabolic and respiratory acidosis
  - Drugs (Cyclosporine – **Alcohol** – Nicotinic acid – Thiazides – **Lasix** – Ethambutol – Aspirin (<325mg) – Pyrazinamide

Uric acid is the end product of purine degradation.

The human species lacks uricase – which oxidizes uric acid to more soluble allantoin.

Interestingly, we have the gene for uricase but it is inactive.

Hypothesized to be an evolutionary development as uric acid has potent antioxidant and free radical scavenger functionality.

Underexcretion Pathway

Renal Elimination of Uric Acid
Operationally-Defined, 4-Component Model of Renal Uric Acid Handling

Glomerulus
- Glomerular filtration
  - 100%

Proximal convoluted tubule
- S1
  - 0%-2%
- S2
  - 98%-100% Reabsorption
- S3
  - 50%
  - 40%-48% Reabsorption
  - 8%-12%

Excretion
- Net reabsorption of 90% of filtered uric acid

The genetics of hyperuricemia and gout - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-uric-acid-transportasome-Urate-transporters-in-renal-proximal-tubules-are-involved-in_fig2_230791101
What Works for Gout?

Adherence to gout management is very low compared to other chronic diseases.

Studies show 50-80% of patients stop taking ULT at about 12 months.

Knowledge about gout and its treatment is lacking, both in patients and HCPs.

Gout education increases compliance dramatically (adherence at 1 year ↑ 40-70%, 85% adherence at 5 years).

Patient Education
Systematic review of RCTs evaluated interventions that improve adherence

Education on pathogenesis, co-morbidities and management of gout → increased adherence
<table>
<thead>
<tr>
<th>Hyperuricemia is primarily genetically driven – patient should not be ashamed or blame themselves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout requires long-term treatment → goal is to reduce sUA → eliminate substrate for gout attacks</td>
</tr>
<tr>
<td>Lowering sUA initially may lead to gout flares → goal is to eliminate crystal burden → no more attacks!</td>
</tr>
<tr>
<td>NSAIDs, steroids, colchicine treat acute inflammation but do not treat gout/sUA</td>
</tr>
<tr>
<td>Treatment is <strong>important</strong> → increased frequency of flares, affected joints → permanent/deforming joint damage</td>
</tr>
</tbody>
</table>

**Patient Education Talking Points**
TABLE 1 What should I tell my gout patients?

**Causes and consequences of gout**

- We know its cause: deposition of urate crystals in and around joints.
- Crystals form when sUA concentrations rise above the critical saturation point.
- In people with persistently raised sUA concentrations, crystals slowly but continuously accumulate without causing symptoms initially.
- When sufficient crystals have formed, some occasionally spill out into the joint cavity, triggering severe inflammation and presenting as an acute attack.
- Over many years, acute attacks can increase in frequency and spread to involve other joints.
- In addition to acute attacks, continuing crystal deposition might eventually result in hard, slowly expanding lumps of crystals (tophi) that can cause pressure damage to the joints and can appear as lumps under the skin.
- In some people, tophi could result in irreversible joint damage and cause regular chronic pain on using the joints.
- Reduction and maintenance of sUA concentrations below the saturation point stops production of new crystals and encourages existing crystals to dissolve, so eventually there are no crystals and therefore no gout.
Explanation of risk factors that elevate sUA concentrations above the saturation point

Hereditary factors result in some people having relatively inefficient renal excretion of UA.
High BMI; the majority of UA is made by the cells, and this production increases with obesity.
A purine-rich diet; around one-third of uric acid comes from the diet.
Drugs (e.g. diuretics) can reduce the kidney’s ability to excrete uric acid.
Chronic renal impairment.
Gout is associated with obesity, hypertension, hyperlipidaemia, diabetes, myocardial infarction, chronic renal impairment and kidney stones.
Treatment

Treat acute attacks of gout with colchicine, NSAIDs or CSs, rest and ice-packs.
Explain that ULT can eventually eliminate the crystals and cure gout.
Consider prophylaxis to prevent acute attacks of gout when starting ULT.
There is a need for slow, upward titration of ULT to reduce provocation of attacks.
There is a need for individualized dosing of ULT to achieve the desired sUA concentration (treat to target).
Dietary and lifestyle factors can also reduce urate concentrations, but they are ancillary to ULT.

sUA: serum uric acid; ULT: urate-lowering treatment.
Improving disease education in people with gout

- Include family/caregiver in education
- Consider impact of age, gender, ethnicity, language, health literacy and socio-economic status
- Multidisciplinary approach with optimal provider communication and effective provider education
- Explore and address patient-identified knowledge gaps and concerns/barriers to treatment
- Ongoing, spaced teaching
- Match modality with patient preference
- Use opportunities in hospital and urgent care settings to plan long-term treatment strategies

Optimal gout patient outcomes
Is ULT warranted?
- Need established diagnosis of gout (crystal proven or supported by elevated uric acid (>6 mg/dL or 360 mmol/L), consistent clinical presentation, and/or supporting imaging findings) + any of the following
  - Flare Frequency: ≥ 2 in last year; ≥ 1 with concomitant CKD stage 2 or higher
  - Tophi: presence on exam or imaging.
  - Urate nephrolithiasis
- Strong Considerations:
  - Young age ≤ 40
  - Very high SUA level (e.g. >8 mg/dL or 0.475 mmol/L)
  - Comorbidities that warrant ongoing diuretic use

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Establish goal SUA
< 6 mg/dL (0.475 mmol/L); consider < 5 mg/dL (0.300 mmol/L) with severe disease*

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Flare Prophylaxis
- Begin daily colchicine, or low dose steroid (e.g. < 10 mg prednisolone daily), or low dose NSAID as alternative.
- Initiate 1-2 weeks prior to starting ULT; continue for the longer of: 6 months after reaching SUA goal, or 3 months after last attack.

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Initiate urate lowering therapy
Assess comorbidities, side effect profile, disease severity and prior treatments to guide drug selection.
1. **Allopurinol**: Recommended first line.
   - Begin 100 mg daily**
   - Increase 50-100 mg every 2-4 weeks
   - Titrate to SUA goal

2. **Febuxostat**: Alternative first line agent.
   - Begin 40 mg daily
   - Titrate to 80 mg daily

3. **Probenecid**: Consider as if allopurinol or febuxostat contraindicated, or add on

4. **Lesinurad**: Add on therapy to allopurinol or febuxostat.

5. **Pegloticase**: Severe disease or in those who have contraindications or treatment failure with above drugs*

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**Monitor Therapy**
- Check SUA, liver and kidney every 1-2 months while titrating therapy to target.
- Once at SUA goal and stable disease, continue ULT; check SUA every 6-12 months
- Assess diet, evaluate status of comorbidities (e.g., hypertension, hyperlipidemia, overweight/obesity, cardiovascular disease, insulin resistance

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**Failure to achieve goal SUA with # 1 or 2?**
- Assess patient compliance
- Consider:
  - Switch to other first line therapy
  - Addition of addition agent (#4 or 5)
  - Rheumatology referral
Gout – Management

Dietary
- Avoid purine-rich foods
- Meats (esp organ meats – liver, kidney, etc.)
- Seafood (esp shellfish, sardines/anchovies)
- Avoid excess fructose (sodas, fruit juices)
- Vitamin C, reduced-fat dairy, tart cherries – reduce gout risk
- Purine-rich vegetables (rich green leafy i.e. spinach) not associated with gout risk

Do not generally treat asymptomatic hyperuricemia
- only ~1/10 have gout
- Uric acid >10mg/dL → 50% have gout
- Some suggest treating hyperuricemia to reduce risk of nephrolithiasis but no consensus
Colchicine

Acute – 1.2mg → 1 hr → 0.6mg

Prophylactic – 0.6mg daily
Uricosurics

Probenecid

• Inhibits proximal tubule urate reabsorption
• Avoid in CKD, nephrolithiasis, elderly
• Not commonly used as it is generally less effective and more limitations
Lesinurad

Fig. 6 Lesinurad blocks URAT1 and OAT4 to enhance fractional excretion of uric acid and reduce serum urate levels. This diagram of a nephron depicts the location of urate transporters within the proximal tubule epithelial cell, and the mechanism of action of lesinurad compared to benzbramarone and probenecid. Lesinurad inhibits urate reabsorptive importers URAT1 and OAT4, and the inhibition of OAT4 may counteract postulated OAT4-dependent diuretic-induced hyperuricemia. Benzbramarone specifically inhibits URAT1 but not OAT4. Probenecid nonspecifically inhibits URAT1, OAT4, and other OAT family members, leading to drug-drug interactions involving OAT1 and OAT3. At physiologically relevant concentrations, none of these compounds inhibits GLUT9, another transporter that is important for the renal reabsorption of urate [18–21]
Lesinurad

Inhibits function of (URAT1, OAT4) ≠ reabsorption of uric acid in the kidney

Approved for combination therapy with an XOI, not monotherapy

Patient Related Outcome Measures 2018:9 231–238
Allopurinol

- Allopurinol Hypersensitivity Syndrome (0.1%-0.4%)
- More common in patients who had maculopapular rash 2/2 allopurinol (5-10%)
- Caution in patients with CKD and/or on diuretics
- Clinical: rash, fever, eosinophilia, hepatic necrosis, leukocytosis, worsening renal function
- Tx: high dose steroids and dialysis
- Start at 50mg with slow up titration in higher risk patients

Febuxostat

- 40mg – 80mg (can use higher doses)
- More expensive than allopurinol
- Safe in patients who had AHS
- Hepatic clearance

**Xanthine Oxidase Inhibitors**
Allopurinol & Febuxostat: MoA

Xanthine oxidase (X.O.) inhibitors

https://newdrugsprovels.org/2016/07/11/febuxostat/
Pegloticase

Pegylated Recombinant Uricase

- Uric Acid → Allantoin
- Pegylated: reduces immunogenicity (compared to rasburicase)
- 8mg Q2weeks
- Check uric acid before each infusion to ensure appropriate uric acid lowering – if levels >6.0 → concern for pegloticase Ab and loss of efficacy, increased risk of anaphylaxis
- Don’t use ULT concurrently as can mask uric acid increase when Ab formation occurs
Dual MOA **without** affecting XO

- Inhibits IL-1β expression (anti-inflammatory)
- Blocks URAT1, OAT4, OAT10 transporters (uricosuric)

No established superiority to XOIs or anti-inflammatory agents, but single-drug regimen could improve adherence

Combination therapy with XOIs is safe and effective
Thank You