Knee pain treatment comparison

Treatment options

Treatment	Typical Duration of Effect	WOMAC Change	VAS Change	Retreatment Rate	Success Rate	Side Effects	Notes
NSAIDs (oral/topical)	While taken[1] [2]	↓ ~10–20%[1] [2]	↓ 1–2 pts[1] [2]	Continuous[1] [2]	40–60% achieve MCID pain relief[1] [2]	GI bleeding, renal dysfunction, ↑ CV risk	Symptomatic only, no structural benefit[1] [2]
Intra-articular corticosteroids	4–6 wks (up to 3 mo)[3]	↓ ~10–20 pts[3]	↓ ~2 pts[3]	Every 3–4 mo[3]	50–60% short-term responders at 4–6 wks[3]	Flare, infection (rare), systemic hyperglycemia	Quick but short-lived relief. **Repeated use linked to cartilage loss** on MRI[3]
Hyaluronic Acid (HA)	3–6 mo[4] [5] [6] [7]	↓ ~10–15 pts[4] [5] [6] [7]	↓ ~1–2 pts[4] [5] [6] [7]	Every 6–12 mo[4] [5] [6] [7]	50–60% OMERACT–OARSI responders at 6 mo[4] [5] [6] [7]	Local pain, pseudoseptic reaction (rare)	Evidence mixed; may work better in mild–moderate OA[4] [5] [6] [7]
Platelet-Rich Plasma (PRP)	6–12 mo (sometimes >1 yr)[6] [8] [14] [15]	↓ ~15–25 pts[6] [8] [14] [15]	↓ ~2–3 pts[6] [8] [14] [15]	Annual if repeated[6] [8] [14] [15]	60–75% responders at 6–12 mo[6] [14] [15]	Pain/swelling post-injection, rare infection	Multiple RCTs show superiority over HA/steroids. Better response in earlier OA[6] [14] [15]
Physical Therapy & Exercise	Ongoing (requires adherence)[9]	↓ ~10–20%[9]	↓ ~1 pt[9]	Needs maintenance[9]	50–60% clinically improved[9]	Muscle soreness, fall risk (frail pts)	First-line guideline recommendation. Improves function and delays surgery[9]
Weight Loss (≥10% body weight)	Sustained if maintained[10]	↓ ~10–20 pts[10]	↓ ~1–2 pts[10]	Lifestyle dependent[10]	50–70% with ≥10% loss[10]	None	greater loss → greater improvement, but **difficult to achieve for some pts**[10]
Total Knee Arthroplasty (TKA)	10–20 yrs durability[11]	↓ 30–50 pts[11] [12] [13]	↓ 4–6 pts[11] [12] [13]	Revision 5–10% at 10 yrs[11]	82–90% satisfied or much improved[11] [12] [13]	Surgical risk (infection, DVT/PE, loosening, persistent pain in ~20%)	**Gold standard** for end-stage OA. Outcomes worse in morbid obesity (BMI ≥40)[11] [12] [13]

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Knee pain
New and upcoming treatment comparison

New and upcoming treatment options

Treatment	Typical Duration of Effect	WOMAC Change	VAS Change	Retreatment Rate	Success Rate	Side Effects	Notes
Denosumab (osteoclast inhibitor; cartilage-targeting)	6–12 mo (pilot/RCTs)[1,2]	No significant change[1,2]	No significant change[1,2]	Not established	No proven efficacy[1,2]	Hypocalcemia, rare ONJ/atypical fracture	DISKO and pilot RCTs showed **no improvement in WOMAC pain/function or MRI cartilage outcomes**. Development **halted.**
Tanezumab (anti–NGF; pain-targeting)	Up to 24 wks (RCTs)[3–6]	↓ ~10–15 pts[3–5]	↓ ~2–3 pts[3–5]	Not FDA approved	~50–60% responders in RCTs[3–5], not used clinically	Paresthesia, hypoesthesia, **RPOA 1.4–2.8%**[3–6] ***	Significant pain reduction, but FDA rejected due to **risk–benefit unfavorable** (RPOA progression).[3–6]
GLP-1 receptor agonists (e.g., semaglutide 2.4 mg weekly)	68 wks (STEP-9 RCT)[7–9]	↓ ~14 pts[7]	↓ ~1–1.5 pts (rescaled)[7]	Continuous therapy	Higher OMERACT–OARSI responder rate vs placebo[7]	GI intolerance (nausea, vomiting), discontinuation ~6–7%[7]	Large functional/pain benefit in obese knee OA, likely due to **weight loss + anti-inflammatory effect**. First high-quality RCT in OA[7–9].
Stem cell injections (IA-MSCs)	6–12 mo in RCTs/meta-analyses[10–13]	↓ ~12–18 pts[10–13] (in some studies); others **no difference vs HA/steroid**[10–13]	↓ ~1.5–2 pts[10–13] (variable)	Protocol-dependent (single vs repeated)[12]	Variable; low-certainty benefit[10–13]	Local pain/swelling; heterogeneity in prep	No consistent MRI or structural improvement. Evidence heterogeneous and **low certainty**[10–13].
Duloxetine (SNRI, oral)	While taken[14]	↓ ~17.5 pts (0–100 WOMAC pain)[14]	↓ ~1–2 pts[14]	Continuous	~50–60% in moderate OA pain[14]	Nausea, fatigue, dry mouth, dizziness[14]	Cost-effective and beneficial even when given to **all patients**; **benefit may be greater in those with depression**[14].

***RPOA incidence** = (# adjudicated RPOA cases / # participants dosed) ×100; includes Type 1 (JSW loss ≥2 mm) and Type 2 (destructive arthropathy); placebo ~0–0.4%

Limitations of Emerging OA Therapy Trials

🔹 Denosumab (osteoclast inhibitor)

- Studied mainly in **symptomatic knee OA with bone marrow lesions** (BMLs).
- **Small pilot trials** (n≈50–150 total across studies).
- **Short duration** (6–12 months).
- No clear stratification by **Kellgren–Lawrence grade**.
- Did not enrich for obesity/BMI → no insights into obese subgroups.
- No long-term structural endpoints achieved.

🔹 Tanezumab (anti–NGF, pain-targeting)

- Phase 3 RCTs enrolled **moderate-to-severe knee or hip OA** (KL grade 2–3).
- Large trials (n≈3,000 across programs).
- **Excluded severe comorbidities**
- No morbid obesity subgroup analysis (patients with BMI >40 often excluded).
- Safety signal: **rapidly progressive OA (RPOA)** in ~2% → halted development.
- Maximum duration 24 wks → no long-term functional or structural follow-up.

🔹 GLP-1 receptor agonists (semaglutide 2.4 mg, STEP-9)

- Population: **obese patients (BMI ≥30) with knee OA**, KL 2–3. n≈407 randomized.
- Duration: **68 weeks** (longer than most OA symptom-modifying drug trials).
- Primary endpoint: **WOMAC pain** — not VAS.
- **Exclusion:** non-obese OA patients (limits generalizability).
- Benefit may be **partly mediated by weight loss**, not direct joint action.
- No structural outcomes (MRI/cartilage) reported.

🔹 Stem cell injections (MSC, IA delivery)

- Heterogeneous: trials differ in **cell source** (bone marrow, adipose, umbilical), dose, and protocol.
- Most RCTs small (n=20–100). Meta-analyses pool ~1,000 pts but with **high heterogeneity**.
- Duration: mostly **6–12 months**, limited long-term follow-up.
- OA severity: typically **KL 2–3**, very few KL 4 (end-stage OA excluded).
- Often compared against HA or steroids (not true placebo), leading to **uncertain incremental benefit**.
- MRI/structural endpoints **inconsistent or negative**.
- **Industry-sponsored bias** suspected in some positive studies.

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