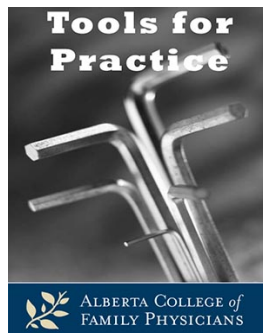


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**Reviewed: August 13, 2016**  
**Evidence Updated: New evidence**  
**Bottom Line: No change**  
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## **Viscosupplementation (Hyaluronic Acid or Hylan): Cushioning the Blow (To Your Wallet)?**

**Clinical Question: Do injections of viscosupplements (hylan or hyaluronic acid) improve symptoms of knee osteoarthritis?**

**Bottom Line: Research on viscosupplementation (hylan or hyaluronic acid) for knee osteoarthritis has frequently been of poor quality and has exaggerated effectiveness. The best evidence indicates no meaningful benefit (if any at all) with potential adverse events (including cost).**

**Evidence:** At least eight systematic reviews. Focus on the best and consider others.

- Rutjes 2012:<sup>1</sup> 89 randomized controlled trials (RCTs) with 12,667 patients (mean age 63), median follow-up 16 years.
  - Reduction in pain (at three months), effect size -0.37 (-0.28 to -0.46).
    - Just reached minimally important clinical benefit (-0.37 = nine mm on 100 mm pain scale).
  - But many issues:
    - Higher quality studies (>100 patients, proper randomization, or blinded outcome assessor) found no clinically meaningful improvement in pain or function.
    - Publication bias: Negative trials less likely to be published. Five of six unpublished studies provided data and showed no effect.
  - Adverse events increased:
    - Serious adverse events: Relative risk 1.41 (1.02-1.97).
    - Dropouts due to adverse events: Relative risk 1.33 (1.01-1.74).
- Bannuru 2015:<sup>2</sup>
  - Versus intra-articular placebo: Effect size -0.34 (-0.26 to -0.42).
  - No difference versus intra-articular corticosteroid: Effect size -0.02 (+0.12 to -0.17).

- Large placebo effect (expectation bias) from intra-articular administration of medications.
  - Intra-articular placebo versus oral placebo: Effect size -0.29 (-0.04 to -0.54).
- Six other systematic reviews<sup>3-8</sup> (with between seven-76 RCTs each) found.
  - Similar results.<sup>3,4</sup>
  - No difference in patients reporting global improvement.<sup>5</sup>
  - Placebo injections similar to viscosupplementation.<sup>6</sup>
  - Clinically meaningful difference not discussed or rarely attained.<sup>3-8</sup>
  - Higher quality studies showed smaller benefit.<sup>3,7</sup>
  - Patients >65 years with more advanced radiographic osteoarthritis may be less likely to benefit.<sup>8</sup>

### Context:

- While the conclusions of some systematic reviews are positive,<sup>5-8</sup> these ignore clinically meaningful outcomes and/or include poor-quality, biased studies.
- Systematic review examining the timing of viscosupplementation effect.<sup>9</sup>
  - Peak effect at eight weeks: effect size -0.34 (-0.02 to -0.67) for high-quality studies.
  - Still less than 0.37 minimally important clinical difference.<sup>1</sup>
- Systematic review comparing hylan to hyaluronic acid found no difference (except hylan may have more adverse events).<sup>10</sup>
- Viscosupplementation (one-three injections) costs \$285-500.

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