GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

A Matter of Time

Bedtime vs Morning BP Medications in Frail Elders

Orforglipron

The Tiny Molecule Taking on a Big Diabetes Challenge

Cracking the Collagen Code

Can Supplements Soothe Osteoarthritis Pain?

FPIN
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A Matter of Time: Bedtime vs Morning BP Medications in Frail Elders

Bedtime vs Morning Antihypertensive Medications in Frail Older Adults

Garrison SR, Youngson ERE, Perry DA, et al. Bedtime vs Morning Antihypertensive Medications in Frail Older Adults: The BedMed-Frail Randomized Clinical Trial. *JAMA Netw Open*. 2025;8(5):e2513812. Published 2025 May 1. doi:10.1001/jamanetworkopen.2025.13812

KEY TAKEAWAY: Administration of a once daily antihypertensive at bedtime does not significantly reduce all-cause mortality or major cardiovascular events compared to morning doses in older adults in nursing homes.

STUDY DESIGN: Pragmatic, cluster-randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The right timing of antihypertensive therapy between morning and bedtime has been debated. Some studies demonstrate improved cardiovascular outcomes with bedtime dosing due to better nocturnal blood pressure control. However, prior research has demonstrated conflicting outcomes, while excluding older adults. As this population tends to have the highest risk of falls, polypharmacy, and cognitive impairment, this study aimed to evaluate if bedtime antihypertensive provide benefit or harm.

PATIENTS: Frail older nursing home residents using at least one daily antihypertensive medication

INTERVENTION: Bedtime administration

CONTROL: Morning administration

PRIMARY OUTCOME: All-cause death or major cardiovascular events

Secondary Outcome: Falls, fractures, cognitive deterioration, skin ulcers

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from a nursing home in a designated supported living level four and long-term care facilities.
- 85% of participants had dementia, and 50% had diabetes or CKD.
- The median length of stay in the facility was 1–1.2 years.
- Patients were randomized to once daily administration of antihypertensive medication either at bedtime or in the morning.
- Medications included calcium channel blockers, ace inhibitors, angiotensin receptor blockers, beta-blockers, and diuretics.
- The dose and frequency remained the same between groups.
- The primary outcome measured all-cause death or major cardiovascular events using the administrative health data, including diagnostic codes from hospital discharge summaries, emergency department (ED) visits, and provincial death registry records.
- Secondary outcomes were measured using the following:
  - Falls that were recorded occurred 30 days before assessment.
  - Skin ulcers were identified as stage 2–4 partial or full thickness.
  - Cognitive decline was assessed as a change in status based on nurse judgment.
  - Non-Vertebral Fractures were assessed with ICD 10 codes at ER and Hospital admissions.

INTERVENTION (# IN THE GROUP): 394

COMPARISON (# IN THE GROUP): 382

FOLLOW-UP PERIOD: Length of time

RESULTS:

Primary Outcome –

- Bedtime antihypertensive administration did not significantly reduce all cause death or major cardiovascular events compared to morning administration (adjusted hazard ratio [aHR] 0.88; 95% CI, 0.71–1.1).

Secondary Outcome –

- Bedtime administration reduced all-cause unplanned hospitalizations and emergency department visits (aHR 0.74; 95% CI, 0.57–0.96).
- Bedtime antihypertensive administration did not significantly affect the number of fractures, falls, cognitive deterioration, or skin ulcers compared to morning administration.

LIMITATIONS:

- The results may not be generalizable to healthy adults or patients not in institutions.
- Most death were non-cardiovascular, limiting data on the benefits of cardiovascular events.
- The study was open label, allowing for bias.
- The data was collected at a single time point.
- Cognitive decline was assessed based on nurse's judgements and may not be accurate.

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Orforglipron: The Tiny Molecule Taking on a Big Diabetes Challenge

Orforglipron, An Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

Rosenstock J, Hsia S, Nevarez Ruiz L, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes. *N Engl J Med*. 2025;393(11):1065-1076. doi:10.1056/NEJMoa2505669

KEY TAKEAWAY: Orforglipron effectively lowers hemoglobin A1c (HbA1C) and reduces body weight compared to lifestyle modification alone in patients with type 2 diabetes mellitus (T2DM) who do not respond to diet and exercise.

STUDY DESIGN: Multicenter, double-blind, randomized, placebo-controlled phase 3 trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have gained popularity for their effectiveness in controlling glucose levels, as well as addressing risk factors and potential comorbidities of diabetes. Most GLP-1RAs are injectables with semaglutide as the only oral option requiring dietary restrictions. Orforglipron is an orally available GLP-1RA that can be taken independent of meal or water intake, suggesting the potential for improved patient compliance and greater convenience in managing diabetes. The study aimed to evaluate the effectiveness and safety of orforglipron therapy in people with T2DM ineffectively managed with diet and exercise alone.

PATIENTS: Adults with T2DM

INTERVENTION: Orforglipron

CONTROL: Placebo

PRIMARY OUTCOME: Change in HbA1c

Secondary Outcome: Proportion achieving HbA1C <7%, change in body weight, non-high-density lipoprotein (HDL) cholesterol, triglyceride levels

METHODS (BRIEF DESCRIPTION):

- 875 candidates were assessed for eligibility, 559 were enrolled from study centers in five countries, and 526 participants (94%) completed the trial.
- Participants ≥18 years old had a diagnosis of T2D with HbA1c of 7–9.5%, a body mass index (BMI) ≥23, no use of glucose-lowering agents in the previous three months, and current management being only lifestyle modifications, diet and exercise.
- Patients with a history of pancreatitis, liver disease or significant liver or kidney function abnormality were excluded from the study.
- Patients were randomized using interactive web response system to 1:1:1:1 over 40 weeks (orforglipron 3 mg, 12 mg, 36 mg and placebo).
- Orforglipron was started at 1 mg for the three non-placebo arms then titrated every four weeks to reach target dose.
- Rescue medications were allowed for severe persistent hyperglycemia and HbA1c ≥8.5% after week 24.
- The primary outcome (change in HbA1c) was measured using two pre-specified estimands which included intention to treat and per-protocol.
- Analysis of covariance (ANCOVA) was used for assessment of continuous outcomes.
- Binary outcomes, such as HbA1c <7%, 6.5%, and 5.7%; weight loss with ≥5%, ≥10% or ≥15% of body weight; treatment discontinuation; presence/absence of certain side effects were analyzed using logistic regression.
- Safety endpoints were analyzed for every participant who received at least one treatment dose.

INTERVENTION (# IN THE GROUP):

- Orforglipron 3 mg: 143
- Orforglipron 12 mg: 137
- Orforglipron 36 mg: 141

COMPARISON (# IN THE GROUP): 138

FOLLOW-UP PERIOD: 42 weeks

RESULTS:

Primary Outcome –

- Orforglipron improved HbA1c compared to placebo at all doses:
  - 3 mg orforglipron (estimated mean difference [MD] –0.83%; 95% CI, –1.1 to –0.56)
  - 12 mg orforglipron (estimated MD –1.1%; 95% CI, –1.3 to –0.79)
  - 36 mg orforglipron (estimated MD –1.1%; 95% CI, –1.3 to –0.81)

Secondary Outcome –

- Orforglipron improved target HbA1c <7.0% compared to placebo:

    - 3 mg orforglipron (estimated MD 35%; 95% CI, 25–46)
    - 12 mg orforglipron (estimated MD 40%; 95% CI, 29–51)
    - 36 mg orforglipron (estimated MD 40%; 95% CI, 29–50)
- Orforglipron reduced body weight compared to placebo at 12 mg and 36 mg:
    - 12 mg orforglipron (estimated MD –4.1%; 95% CI, –5.4 to –2.7)
    - 36 mg orforglipron (estimated MD –5.9%; 95% CI, –7.4 to –4.4)
- Orforglipron improved triglyceride levels compared to placebo at 12 mg and 36 mg:
    - 12 mg orforglipron (estimated MD –11%; 95% CI, –19 to –3.0)
    - 36 mg orforglipron (estimated MD –10%; 95% CI, –18 to –2.2)
- Orforglipron improved non-HDL cholesterol levels compared to placebo at 36 mg (estimated MD –9.3%; 95% CI, –14 to –4.5).

LIMITATIONS:

- The study was industry sponsored by Eli Lilly.
- The study had a narrow population that included participants with early T2DM on diet and exercise only.
- The study had a short treatment duration of 40 weeks.
- The study had no active comparator.

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Cracking the Collagen Code: Can Supplements Soothe Osteoarthritis Pain?

Efficacy and Safety of Collagen Derivatives for Osteoarthritis: A Trial Sequential Meta-Analysis

Liang CW, Cheng HY, Lee YH, Liao CD, Huang SW. Efficacy and Safety of Collagen Derivatives for Osteoarthritis: A Trial Sequential Meta-analysis. *Osteoarthritis Cartilage*. 2024;32(5):574-584. doi:10.1016/j.joca.2023.12.010

KEY TAKEAWAY: Collagen supplements moderately improve pain and function in adults with osteoarthritis (OA) without increasing adverse events, although study heterogeneity and small-study bias may limit generalizability.

STUDY DESIGN: Systematic review and meta-analysis of 25 randomized controlled trials (RCTs) (N=2,586)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to short follow-up times, limited power of sub-group analysis, and questionable meaningful benefit)

BRIEF BACKGROUND INFORMATION: OA can lead to chronic pain that is often disabling. OA is commonly managed with non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. Collagen derivatives (collagen hydrolysate, undenatured collagen II, collagen peptides, polymerized collagen) are advertised as nutritional supplements for joint health, but their efficacy has been unclear. This review aimed to evaluate if collagen improves OA symptoms safely and effectively.

PATIENTS: Adults with OA

INTERVENTION: Daily oral collagen supplementation

CONTROL: Placebo or standard therapy

PRIMARY OUTCOME: Pain

Secondary Outcome: Physical function, safety outcomes

METHODS (BRIEF DESCRIPTION):

- Included studies enrolled adults with diagnosed OA (mainly knee OA), with most participants between 50–70 years old.
- Excluded studies did not meet diagnostic criteria for OA or had <20 patients per treatment arm (to reduce small study bias).
- Trials assessed oral collagen derivatives including hydrolyzed collagen (collagen hydrolysate), undenatured type II collagen (UC-II), collagen peptides or composite products. Dose ranged from 1.2–10 g/day for hydrolyzed collagen and 10–40 mg/day for UC-II. Duration of treatment ranged from 8–24 weeks.
- Most control groups received placebo capsules or powders. Some studies allowed continued standard therapy (e.g. NSAIDs, acetaminophen) in both groups for ethical reasons.
- Primary outcomes were pain improvement and secondary outcomes were physical function and safety outcomes.
- Pain was assessed using a variety of instruments across studies and was reported in this review using standardized mean differences (SMD) and Visual Analog Scale (VAS). The minimal clinical difference (MCID) for pain on a 0–100 mm VAS is typically 9–12 mm.
- Function was assessed using various validated tools and numeric rating scales across included studies. Outcomes were pooled and reported using SMDs, and Hedges' g was used to estimate effect sizes, with thresholds of 0.2, 0.5 and 0.8 interpreted as small, moderate and large clinical effects respectively.
- Safety outcomes included all-cause withdrawal and adverse events, reported as event counts and analyzed using risk ratios with 95% confidence intervals.
- GRADE methodology was used to evaluate the certainty of evidence for the outcomes. Certainty was rated by high, moderate, low, or very low based on five domains: Risk of bias, inconsistency, imprecision, indirectness, and publication bias.
- Heterogeneity for continuous outcomes was evaluated using tau squared values, with thresholds applied to interpret low (0.04), moderate (0.09), or high (0.16) variability across studies.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (8–24 weeks)

RESULTS:

Primary Outcome –

- Collagen supplements significantly improved pain compared to control (25 studies, N=2,856; pooled standardized mean difference [SMD] –0.35; 95% CI,

–0.48 to –0.22), indicating a moderate effect with moderate certainty.

- This corresponds to a non-clinically significant pain reduction on the VAS (8.5 mm; 95% CI, –12 to –5.4 mm, τ^2=.05), with moderate certainty.

Secondary Outcome –

- Collagen supplementation increased physical function compared to the control (24 studies, n=2,647; SMD –0.31; 95% CI, –0.41 to –0.22), corresponding to a functional improvement of (–7.8 points; 95% CI, –10 to –5.5; τ^2=.01) with high certainty.
- No statistically significant difference in all cause withdrawal or adverse events.

LIMITATIONS:

- There was moderate heterogeneity in the studies assessing pain outcomes.
- Many of the included trials had short follow up durations (<6 months), leaving the long-term efficacy of collagen supplements unclear.
- There was substantial variability in the types, formulations, and doses of collagen used across the studies, which may be difficult for generalizability.
- Improvement was just below the MCID, suggesting questionable clinically meaningful benefit.

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