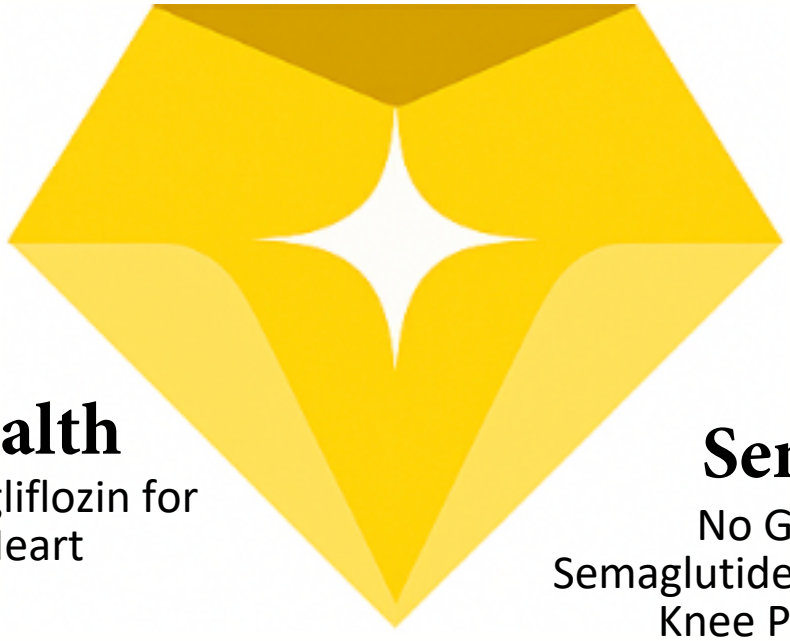
GOOD EVIDENCE MATTERS

GEMs of the Week



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Volume 5 Issue 29

Multimodal Approaches to Pain: Do Antidepressants Have a Place?

Antidepressants for Pain Management in Adults with Chronic Pain: A Network Meta-Analysis

Birkinshaw H, Friedrich CM, Cole P, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. *Cochrane Database Syst Rev*. 2023;5(5):CD014682. Published 2023 May 10. doi:10.1002/14651858.CD014682.pub2

KEY TAKEAWAY: Duloxetine 60 mg provided the most substantial pain relief and decreased pain intensity compared to other antidepressants.

STUDY DESIGN: Network meta-analysis (N=28,664)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: In 2021, nearly 21% of U.S. adults experienced chronic pain (CDC). Treatment options for pain are diverse, including analgesic medications, manual medicine, exercise, psychological therapy, and surgery. Antidepressants have also been used to manage chronic pain; however, there are few head-to-head comparisons between medications rendering clinical guidance confusing.

PATIENTS: Adults with chronic pain

INTERVENTION: Various antidepressants

CONTROL: Placebo, alternative antidepressant/dose, alternative therapy

PRIMARY OUTCOME: Substantial pain relief, pain intensity, and mood

Secondary Outcome: Moderate pain relief, physical function, sleep, quality of life, patient global impression of change (PGIC), serious adverse events

METHODS (BRIEF DESCRIPTION):

- Databases were searched for randomized clinical trials that compared any antidepressant with any comparator.
- Studies included adults ≥18 years old (mean age of 51 years old) with chronic pain on antidepressant treatment, with a study duration of at least two weeks and minimum of 10 participants per arm.
- Studies with headache or migraine as the primary complaint and used non-random selection and non-concealed allocation were excluded.
- Of the 176 total studies, 141 were parallel-arm design and 35 were cross-over design.
- Many studies involved participants with at least one type of chronic pain including fibromyalgia, neuropathic pain, musculoskeletal pain, somatoform/idiopathic pain, gastrointestinal pain, non-cardiac chest pain, burning mouth syndrome, visceral pain, atypical facial pain, phantom limb pain, and pelvic pain.
- Once the study data was extracted, separate analyses were performed. For substantial pain relief and moderate pain relief measurements, odds ratios with 95% confidence intervals were calculated. For continuous data such as pain intensity, standardized mean difference with 95% confidence intervals were used.
    - Substantial pain relief was defined as ≥50% improvement.
    - Moderate pain relief was defined as 30–49% improvement.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (2 weeks to 9 months)

RESULTS:

Primary Outcome –

- Standard and high dose duloxetine resulted in substantial pain relief compared to control:
    - Standard dose (42 trials, n=14,626; odds ratio [OR] 1.9; 95% CI, 1.7–2.2)
    - High dose (42 trials, n=14,626; OR 1.9; 95% CI, 1.7–2.2)
- Standard and high dose duloxetine significantly decreased pain intensity compared to control:
    - Standard dose (42 trials, n=14,626; standardized mean difference [SMD] –0.37; 95% CI, –0.45 to –0.28)
    - High dose (42 trials, n=14,626; SMD –0.31; 95% CI, –0.39 to –0.24)
- Standard and high dose milnacipran significantly decreased pain intensity compared to control:
    - Standard dose (42 trials, n=14,626; SMD –0.22; 95% CI, –0.40 to –0.05)
    - High dose (42 trials, n=14,626; SMD –0.22; 95% CI, –0.39 to –0.06)

- Mirtazipine was most effective for mood compared to control (42 trials, n=14,626; SMD –0.5; 95% CI, –0.78 to –0.22).

Secondary Outcome –

- All antidepressants resulted in moderate pain relief compared to controls:
  - Mirtazapine (40 trials, n=14,208; OR 1.9; 95% CI, 1.5–2.4)
  - Duloxetine (40 trials, n=14,208; OR 1.8; 95% CI, 1.7–1.9)
  - Milnacipran (40 trials, n=14,208; OR 1.7; 95% CI, 1.5–1.9)
  - Esreboxetine (40 trials, n=14,208; OR 1.7; 95% CI, 1.3–2.0)
- Standard and high dose duloxetine increased physical function compared to control:
  - Standard dose (SMD –0.24; 95% CI, –0.32 to –0.18)
  - High dose (SMD –0.23; 95% CI, –0.30 to –0.16)
- Standard and high dose duloxetine improved sleep compared to control:
  - Standard dose (SMD –0.21; 95% CI, –0.30 to –0.12)
  - High dose (SMD –0.14; 95% CI, –0.27 to –0.01)
- Standard and high dose duloxetine improved PGIC compared to control:
  - Standard dose (SMD –0.36; 95% CI, –0.44 to –0.29)
  - High dose (SMD –0.33; 95% CI, –0.40 to –0.26)
- There was no significant difference in quality of life or serious adverse events.

LIMITATIONS:

- The meta-analysis included studies with brief trials and follow-up periods.
- Outcomes were measured subjectively, possibly introducing bias.
- Confounding variables may have affected patient's perceptions of outcomes.
- There was a high risk of bias due to a lack of blinding.
- Significant heterogeneity was present between the studies, limiting the consistency of the findings.

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90 Days of Empagliflozin for a Healthier Heart

The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure: A Multinational Randomized Trial

Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1

KEY TAKEAWAY: Initiating empagliflozin 10 mg daily in hospitalized patients with heart failure (HF) improves 90-day cardiovascular outcomes, including death and recurrent exacerbations, regardless of diabetes status or left ventricular ejection fraction (LVEF).

STUDY DESIGN: Multicenter, double-blind, randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Exacerbation of acute HF is a common cause of hospitalization in older individuals with multiple comorbidities. It can lead to increased mortality and worse quality of life. Historically, there has been a lack of evidence for medications that improve health outcomes or quality of life during the post-discharge period. Whether sodium-glucose cotransporter 2 (SGLT2) inhibitors benefit hospitalized patients during this period is unknown.

PATIENTS: Hospitalized patients with acute or decompensated HF

INTERVENTION: Empagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Clinical benefit

METHODS (BRIEF DESCRIPTION):

- Hospitalized patients ≥18 years old from 118 centers with a primary diagnosis of acute HF were screened.
- Individuals with cardiogenic shock, pulmonary embolism, cerebrovascular accident, or acute myocardial infarction (MI) as the primary trigger for hospitalization were excluded from the study.
- Patients were randomly assigned to receive empagliflozin 10 mg daily or placebo.
- Randomization occurred after at least 24 hours but no later than five days after admission.
- The primary outcome measured the clinical benefit, defined as a composite outcome of time to all-cause death, the number of HF exacerbations, time to first HF exacerbation, and a ≥5 point difference in change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KSSQ-TSS).
    - The KCCQ-TSS is a measurement of symptom frequency and severity in heart failure. Score range from 0–100, with higher scores indicating fewer symptoms and limitations.
- A win ratio was calculated using a non-parametric generalized pairwise comparison for the primary outcome.

INTERVENTION (# IN THE GROUP): 265

COMPARISON (# IN THE GROUP): 265

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Empagliflozin resulted in a greater clinical benefit compared to placebo (win ratio 1.4; 95% CI, 1.1–1.7).

LIMITATIONS:

- The short enrollment window and the requirement for patient stabilization may have excluded older and more severely diseased patients.

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No Gain, No Pain: Semaglutide and Osteoarthritic Knee Pain in Obesity

Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. *N Engl J Med*. 2024;391(17):1573-1583. doi:10.1056/NEJMoa2403664

KEY TAKEAWAY: Semaglutide increases weight loss and improves osteoarthritic knee pain in patients with obesity and knee osteoarthritis (OA).

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity is a significant risk factor for developing knee OA, and weight loss is a key component of managing obesity-related OA. This study aimed to determine if semaglutide, a popular weight loss medication, could be a suitable adjunctive medication to reduce osteoarthritic knee pain in obese patients.

PATIENTS: Patients with obesity and knee OA

INTERVENTION: Semaglutide injection

CONTROL: Placebo injection

PRIMARY OUTCOME: Knee pain and weight loss

Secondary Outcome: Physical functioning, stiffness

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with obesity, knee OA with associated pain, and radiographic evidence of moderate OA in the affected knee were included in the study.
- Exclusion criteria included joint replacement, recent joint injections, recent weight loss medication use, recent bariatric intervention, and a history of diabetes.
- Patients were randomized in a 2:1 ratio to either a semaglutide injection or a placebo injection.
  - Both received identical counseling on diet and exercise.
  - The semaglutide group started on a 0.24 mg weekly dose, which was gradually increased to 2.4 mg weekly.
    - Patients with significant side effects were allowed to continue at a lower dose.
  - Participants were not allowed to use other weight loss medications during the study. They were allowed to use pain medication throughout the study, except for the 72 hours before each assessment.
- The primary outcomes measured weight loss and knee pain.
  - Knee pain was assessed using the pain component of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Scores range from 0–20, with higher scores indicating more pain.
- The secondary outcome measured physical functioning and stiffness. Physical functioning was assessed using:
  - Physical function subscale component of the WOMAC score. Scores range from 0–68, with higher scores indicating worse physical functioning.
  - The physical function score of the Short-Form Health Survey (SF-36). Scores range from 0–100, with higher scores indicating better physical functioning.
- Knee stiffness was measured using the subscale component of the WOMAC score. Scores range from 0–8, with higher scores indicating more stiffness.

INTERVENTION (# IN THE GROUP): 271

COMPARISON (# IN THE GROUP): 136

FOLLOW-UP PERIOD: 68 weeks

RESULTS:

Primary Outcome –

- Semaglutide decreased body weight compared to placebo (estimated difference –11 percentage points; 95% CI, –12 to –8.6).
- Semaglutide improved knee pain compared to placebo (between-group difference –14; 95% CI, –20 to –8.3).

Secondary Outcome –

- Semaglutide improved physical functioning via WOMAC scores compared to placebo (between-group difference –15; 95% CI, –20 to –9.3).
- Semaglutide improved physical functioning via SF-36 scores compared to placebo (between-group difference 5.6; 95% CI, 3.1–8.0).
- Semaglutide improved knee stiffness compared to placebo (between-group difference –16; 95% CI, –23 to –8.6).

LIMITATIONS:

- Most enrollees were women, which limits the study's generalizability to other patient populations.
- No assessments determined adherence to lifestyle recommendations throughout the study.
- With a lack of significant follow-up after discontinuation, the persistence of semaglutide's effect cannot be determined.
- The study was funded by Novo Nordisk, a manufacturer of semaglutide.

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Less is More? Evaluating Infrequent Zoledronate for Osteoporotic Fracture Prevention

Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age

Bolland MJ, Nisa Z, Mellar A, et al. Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age. *N Engl J Med*. 2025;392(3):239-248. doi:10.1056/NEJMoa2407031

KEY TAKEAWAY: Infrequent administration of zoledronate can prevent vertebral fractures in postmenopausal women.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Zoledronate infusions can reduce fracture risk in patients at increased risk. It is typically administered at 12–18 month intervals. Zoledronate's effect on bone turnover persists over five years, but the effectiveness of longer interval dosing on fracture prevention is unknown.

PATIENTS: Postmenopausal Women

INTERVENTION: Zoledronate-zoledronate (ZZ) and zoledronate-placebo (ZP)

CONTROL: Placebo-placebo (PP)

PRIMARY OUTCOME: Presence of vertebral fractures

Secondary Outcome: Fragility fracture, any fracture, or major osteoporotic fracture, adverse events

METHODS (BRIEF DESCRIPTION):

- Participants were randomly selected from electoral roll in Auckland, New Zealand and invited by letter to participate.
- Postmenopausal women 50–60 years old with T-scores between 0 and –2.5 and mainly of European descent were included in the study.
- Participants were randomized 1:1:1 into either 5 mg ZZ, 5 mg ZP, or PP.
- The primary outcome measured the presence of vertebral fractures which was defined as a 20% decrease in vertebral height from baseline based on spinal radiographs taken at baseline, five, and 10 years.
- The secondary outcomes measures fragility fractures, any fractures, or major osteoporotic fractures over 10 years.
- A primary analysis was performed in accordance with the intention-to-treat principle with Fisher's exact test, and the results are presented as relative risks with 95% confidence interval.
- Multiple imputation was used for missing data with Bonferroni-adjusted P-values.
- Time-to-first-fracture analyses were modeled with the use of a Cox proportional hazards approach, the log-rank statistic was estimated, and Kaplan-Meier curves were drawn.
- In a secondary analysis the two zoledronate groups were simply pooled and the analyses for fractures repeated.
    - A mixed models approach to repeated measures was used to compare the groups with respect to bone mineral density and bone-turnover markers.

INTERVENTION (# IN THE GROUP):

- ZZ at baseline and five years: 352
- ZP at baseline and five years: 351

COMPARISON (# IN THE GROUP):

- PP at baseline and five years: 351

FOLLOW-UP PERIOD: 10 years

RESULTS:

Primary Outcome –

- ZZ decreased the risk of vertebral fractures compared to PP (relative risk [RR] 0.56; 95% CI, 0.34–0.92; number needed to treat [NNT]=21).
- ZP decreased the risk of vertebral fractures compared to PP (RR 0.59; 95% CI, 0.36–0.97; NNT=22).

Secondary Outcome –

- ZZ and ZP decreased the risk of fragility fractures compared to PP.
    - ZZ (RR 0.72; 95% CI, 0.55–0.93; NNT=13)
    - ZP (RR 0.79; 95% CI, 0.61–1.02; NNT=17)
- ZZ and ZP decreased the risk of any fractures compared to PP.
    - ZZ (RR 0.70; 95% CI, 0.56–0.88; NNT=9)
    - ZP (RR 0.77; 95% CI, 0.62–0.97; NNT=13)
- ZZ and ZP decreased the risk of major osteoporotic fractures compared to PP.
    - ZZ (RR 0.60; 95% CI, 0.42–0.86; NNT=12)
    - ZP (RR 0.71; 95% CI, 0.51–0.99; NNT=18)

- After baseline infusion, uveitis occurred in eight participants and episcleritis occurred in one participant compared to zero in the PP group.
- 11 participants died during the trial. Eight had a myocardial infarction, seven had a stroke, and 49 had cancer, 22 of whom had breast cancer (incidence of each event similar in all groups).

LIMITATIONS:

- Limited generalizability due to only including women 50–60 years old of mostly European descent.
- Secondary outcomes should be interpreted cautiously due to no statistical adjustment.
- Radiographically detected compression fractures may not be clinically significant.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Mind Over Matter: A Regulation of Cues Intervention for Obesity Management

Effect of a Novel Intervention Targeting Appetitive Traits on Body Mass Index Among Adults with Overweight or Obesity: A Randomized Clinical Trial

Boutelle KN, Eichen DM, Peterson CB, et al. Effect of a Novel Intervention Targeting Appetitive Traits on Body Mass Index Among Adults With Overweight or Obesity: A Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(5):e2212354. Published 2022 May 2. doi:10.1001/jamanetworkopen.2022.12354

KEY TAKEAWAY: Programs that utilize regulation of cues (ROC) and ROC plus weight loss programs (ROC+) reduce body mass index (BMI) compared to an active comparator focused on general education, however, neither ROC nor ROC+ approach is more effective than behavioral weight loss (BWL) alone.

STUDY DESIGN: Single-center, parallel-group, blinded, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: BWL programs are the standard for overweight and obesity, but many participants struggle to maintain weight loss over time. Research suggests that appetitive traits, such as food responsiveness (FR) and satiety responsiveness (SR), play a significant role in overeating and weight gain, especially when influenced by environmental cues. However, a few interventions directly target these traits, and there is ongoing investigation into whether such approaches can offer more sustainable weight loss outcomes.

PATIENTS: Adults 18–65 years old with BMI 25–45

INTERVENTION: ROC alone and ROC+

CONTROL: BWL and active comparator (AC)

PRIMARY OUTCOME: BMI

Secondary Outcome: Body fat percentage, loss of control eating

METHODS (BRIEF DESCRIPTION):

- Adults 18–65 years old with a BMI 25–45 without comorbid conditions were included in the study.
  - The participants had a mean age of 47 years, predominantly female (82%) and majority identifying as non-Hispanic White.
- Patients with type 2 diabetes mellitus (T2DM), recent stroke or angina, pregnancy, inability to speak or read English, or relocating soon were excluded from the study.
- Participants were assigned to one of four groups: ROC, ROC+, BWL, or AC.
  - The ROC program aimed to improve management of FR and SR through educational sessions, self-monitoring, practical exercises, and strategies for managing cravings.
  - ROC+ underwent a combined ROC and the BWL program (program explained below). The same session schedule applied as in the ROC group.
  - The BWL program focused on a balanced diet that promoted a weight loss goal of 1–2 lbs per week. Behavior modification focused on stimulus control, self-monitoring, setting goals, managing high risk situations, meal planning, slow eating, problem solving, social support, cognitive restructuring relapse skills, and skills for maintaining weight loss.
  - The AC program provided education on mindfulness, social support, stress management, and basic nutrition but did not include calorie restriction or training related to appetitive traits.
- All participants were required to attend 26, 90-minute group treatments over one year, and all participants had a goal of at least 150 min of moderate to vigorous physical exercise per week in addition to achieving at least 10,000 steps per day.
- The ROC, BWL, and ROC+ groups were provided with pedometers and instructed to self-monitor food caloric intake and physical activities
- 90-minute group treatments included 16 weekly sessions, four biweekly sessions, and six monthly booster sessions.
- The primary outcome measured the change in BMI at baseline, midway, end of treatment (12 months), and during follow-up (18 and 24 months) to assess weight loss success and maintenance over time.
- The secondary outcomes measured the following:
  - Body fat percentage was analyzed using dual-energy X-ray absorptiometry to track body composition changes.

- Loss of eating control was assessed using the Eating Disorder Examination, capturing the frequency and presence of episodes involving loss of control overeating.

INTERVENTION (# IN THE GROUP):

- ROC: 69
- ROC+: 67

COMPARISON (# IN THE GROUP):

- BWL: 69
- AC: 66

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- ROC decreased BMI compared to AC (between-group difference –1.2; 95% CI, –2.1 to –0.25).
- ROC did not have a significant effect on BMI compared to BWL (between-group difference 0.40; 95% CI, –0.55 to 1.4).
- ROC+ decreased BMI compared to AC (between group difference –1.6; 95% CI, –2.4 to –0.67).
- ROC+ did not have a significant effect on BMI compared to BWL (between group difference 0.03; 95% CI, –0.88 to 0.93).

Secondary Outcome –

- ROC did not significantly affect body fat loss compared to AC.
- ROC minimally increased body fat compared to BWL (between-group difference 1.7%; 95% CI, 0.01–3.5).
- ROC+ reduced body fat compared to AC (between group difference –1.6%; 95% CI, –3.7 to –0.22).
- ROC+ did not significantly affect body fat compared to BWL.
- ROC and ROC+ did not significantly affect loss of eating control compared to AC.
- ROC and ROC+ did not significantly affect loss of eating control compared to BWL.

LIMITATIONS:

- Several secondary outcomes lacked statistical analysis, therefore limiting the significance of the results.
- The study relied on self-reported data for physical activity and eating behaviors.
- The sample was limited to treatment-seeking adults, potentially reducing generalizability to broader populations who may not seek weight-loss interventions.
- Follow-up data were collected only for a 12-month period after treatment, which may not capture longer-term weight maintenance or regain.
- The study did not assess other metabolic health markers beyond BMI and body fat percentage, which limits understanding of the interventions' overall health impacts.
- Participants were mostly non-Hispanic White and female, potentially limiting the generalizability to more diverse populations.

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