GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

Week of April 14 - April 18, 2025

## SPOTLIGHT:

# The Answer is CLEAR: Bempedoic Acid

- Solriamfetol: A Promising New Treatment for Adult ADHD
- High-Dose Glucocorticoids for the Treatment of Sudden Hearing Loss
- New Prospects in Treating Alcohol Use Disorder

# The Answer is CLEAR: Bempedoic Acid

**Efficacy and Safety of Bempedoic Acid Among Patients with and Without Diabetes: Prespecified Analysis of the CLEAR Outcomes Randomized Trial**

Ray KK, Nicholls SJ, Li N, et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomized trial. *Lancet Diabetes Endocrinol*. 2024;12(1):19-28. doi:10.1016/S2213-8587(23)00316-9



**KEY TAKEAWAY:** Bempedoic acid reduces the risk of major cardiovascular events (MACE) in patients with diabetes but does not lower the risk of MACE in patients with prediabetes or normoglycemia.

**STUDY DESIGN:** Randomized, double-blind, placebo-controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Previous research demonstrated a reduction in cardiovascular events and lower low-density lipoprotein (LDL) cholesterol with statin therapy; however, it also identified an increased risk of diabetes. This trial evaluated the effects of bempedoic acid on cardiovascular disease (CVD) risk and diabetes incidence.

**PATIENTS:** Patients with diabetes, prediabetes, or diabetes who are statin intolerant with increased CVD risk

**INTERVENTION:** Bempedoic acid

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Cardiovascular efficacy composite of four components

Secondary Outcome: Cardiovascular efficacy composite of three components

**METHODS (BRIEF DESCRIPTION):**

- Patients were selected from 1,250 outpatient primary care clinics from 32 countries.
- Patients included were females >65 years old and males >60 years old who were:
  - Unwilling or unable to take statins
  - Met ≥1 high-risk cardiovascular risk criteria
  - Reynolds risk score >30
  - Coronary artery risk score of >400
  - 10-year coronary risk evaluation of >7.5%
  - Had a diagnosis of type 1 or type 2 diabetes
  - LDL cholesterol of 2.6 mmol/L (100 mg/dL)
- Patients were randomized 1:1 to oral bempedoic acid 180 mg daily and matching placebo.
- Serum laboratory tests were performed every six months to include lipids, high-sensitivity C-reactive protein, hemoglobin A1C (HbA1c), hematology, blood chemistry, urinalysis, and coagulations
- After six months, the central lab notified investigators of patients whose LDL was ≥25% than their baseline who were then given lifestyle modifications.
  - If, after repeat testing, LDL was still above the threshold, the regimen was adjusted to the standard of care.
- The primary outcome examined cardiovascular efficacy occurrence of a four-component MACE.
  - A composite including death from a cardiovascular cause, non-fatal myocardial infarction (MI), non-fatal stroke, or need for coronary revascularization.
- The secondary outcomes examined cardiovascular efficacy occurrence of three-component MACE.
  - A composite including death from cardiovascular causes, non-fatal MI, and non-fatal stroke.
- The intention to treat population of the primary and secondary outcomes groups were statistically analyzed based on glycemic status, diabetes, prediabetes, and normoglycemia.
  - Criteria for diabetes was defined as a history of diabetes, medication for the treatment of diabetes, an HbA1 ≥6.5%, or ≥2 fasting glucose readings of ≥7.0 mmol/L (126 mg/dL).
  - Criteria for prediabetes was defined as an HbA1c of 5.7–6.4%, or ≥1 fasting glucose measurement 5.6 mmol/L (100 mg/dL), but not >7·0 mmol/L (126 mg/dL) before random assignment.
  - Normoglycemic patients met neither of the above criteria.

**INTERVENTION (# IN THE GROUP):** 6,992

**COMPARISON (# IN THE GROUP):** 6,978

**FOLLOW-UP PERIOD:** Median 3.4 years

**RESULTS:**

Primary Outcome –

- Bempedoic acid reduced the risk of the four-component composite of MACE in patients with diabetes (hazard ratio [HR] 0.83; 95% CI, 0.72–0.95).
- Bempedoic acid did not reduce the risk of the four-component composite of MACE in patients with prediabetes (HR 0.94; 95% CI, 0.81–1.1).
- Bempedoic acid did not reduce the risk of the four-component composite of MACE in patients with normoglycemia (HR 0.84; 95% CI, 0.63–1.1).

Secondary Outcome –

- Bempedoic acid reduced the risk of the three-component composite of MACE in patients with diabetes (HR 0.80; 95% CI, 0.68–0.93).
- Bempedoic acid did not significantly impact the three-component composite of MACE in patients with pre-diabetes or who were normoglycemic.

**LIMITATIONS:**

- The study's relatively short duration limited the ability to assess the long-term effects of use on new-onset diabetes.
- The study included those who were unwilling or unable to tolerate statins. This likely included those with negative expectations leading to negative outcomes.
- The study lacked generalizability due to a primarily White patient population.

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# Solriamfetol: A Promising New Treatment for Adult ADHD

**Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults: A Double-Blind Placebo-Controlled Pilot Study**

Surman CBH, Walsh DM, Horick N, DiSalvo M, Vater CH, Kaufman D. Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults: A Double-Blind Placebo-Controlled Pilot Study. *J Clin Psychiatry*. 2023;84(6):23m14934. Published 2023 Oct 9. doi:10.4088/JCP.23m14934



**KEY TAKEAWAY:** Solriamfetol significantly improves attention-deficit/hyperactivity disorder (ADHD) symptoms in adults compared to placebo.

**STUDY DESIGN:** Randomized, double-blind, placebo-controlled pilot study

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to study design and limited sample size)

**BRIEF BACKGROUND INFORMATION:** ADHD involves persistent inattention, hyperactivity, and impulsivity, impairing daily life. This study evaluated the efficacy and cardiac effects of solriamfetol, a selective norepinephrine-dopamine reuptake inhibitor, as current ADHD medications often cause tachycardia.

**PATIENTS:** Adults with ADHD

**INTERVENTION:** Solriamfetol

**CONTROL:** Placebo

**PRIMARY OUTCOME:** ADHD symptoms

Secondary Outcome: Clinical impression, executive function, daily function, sleep quality, self-reported improvement, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Adults 18–65 years old with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) ADHD were included.
- Exclusion criteria included solriamfetol intolerance, unstable health, severe psychiatric disorders, untreated hypertension, pregnancy or nursing, and recent ADHD/catecholaminergic meds.
  - Limited benzodiazepine/sedative use was allowed.
- Participants were randomized to solriamfetol (≤150 mg per day) or placebo.
- The study was conducted remotely with weekly virtual visits.
- The primary outcome measured ADHD symptoms using the Adult ADHD Investigator Symptom Rating Scale (AISRS). Scores range from 0–54, with higher scores indicating more severe ADHD symptoms.
- The following were measured as the secondary outcomes:
  - Clinical impressions were measured using the Clinical Global Impressions (CGI) scale. Scores range from 1–7, with higher scores indicative of worse conditions.
  - Daily functioning was measured using the Global Assessment of Functioning (GAF) scale. Scores range from 1–100, with higher scores indicating better functioning.
  - Executive functioning was measured using the Brief Rating Inventory of Executive Function-Adult (BRIEF-A), which assesses 75 items across nine scales, with higher scores indicating greater difficulties with executive functioning and self-regulation.
  - Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-assessment, with higher scores indicating poorer sleep and more disturbances.
  - Self-reported ADHD symptoms were measured using the Modified ADHD Self-Report Scale (MASRS. Scores range from 0–72, with higher scores indicative of more frequent and severe ADHD symptoms.
  - Adverse events were compared between the two groups.

**INTERVENTION (# IN THE GROUP):** 29

**COMPARISON (# IN THE GROUP):** 29

**FOLLOW-UP PERIOD:** Six weeks

**RESULTS:**

Primary Outcome –

- Solriamferol reduced ADHD symptoms compared to placebo (mean difference [MD] –4.3; 95% CI, –7.7 to –1.0).

Secondary Outcome –

- Solriamferol resulted in “much” or “very much” improved clinical impressions compared to placebo (45% vs 6%, respectively; *P*=.002).

- Solriamferol improved daily functioning compared to placebo (–4.8 vs –0.3, respectively; *P*=.0006).
- Solriamferol improved executive functioning compared to placebo (69% vs 34%, respectively; *P*=.017).
- Solriamferol improved self-reported ADHD symptoms compared to placebo (–11 vs –3.9; *P*=.0047).
- Solriamferol did not result in a significant change in sleep quality or adverse events compared to placebo.

**LIMITATIONS:**

- The small sample size of the study limits the generalizability of the findings to a larger population.
- The study's short duration doesn't reflect the typical ADHD treatment course.
- The study lacked an active comparator for solriamfetol.
- The study was funded by the drug's manufacturer.

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# High-Dose Glucocorticoids for the Treatment of Sudden Hearing Loss

**High-Dose Glucocorticoids for the Treatment of Sudden Hearing Loss**

Plontke SK, Girndt M, Meisner C, et al. High-Dose Glucocorticoids for the Treatment of Sudden Hearing Loss. *NEJM Evid*. 2024;3(1):EVIDoa2300172. doi:10.1056/EVIDoa2300172



**KEY TAKEAWAY:** Intravenous (IV) prednisolone and oral dexamethasone do not improve hearing thresholds compared to oral prednisolone in adults with acute unilateral sensorineural hearing loss.

**STUDY DESIGN:** Three-arm, parallel-group, triple blind randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to a lack of statistical analysis for all secondary outcomes)

**BRIEF BACKGROUND INFORMATION:** In the primary care setting, hearing loss is very common, and it is often not detected and usually undertreated. Systemic glucocorticoids are the primary therapy for idiopathic unilateral sensorineural hearing loss; however, the dosing schedule and form of steroid is still debated. This study aimed to address how systemic glucocorticoids are used in the primary treatment of hearing loss at high and lower doses.

**PATIENTS:** Adults 18–80 years old with unilateral sudden sensorineural hearing loss of unknown etiology

**INTERVENTION:** IV prednisone and oral dexamethasone

**CONTROL:** Oral prednisolone and tapering doses

**PRIMARY OUTCOME:** Change in hearing threshold

Secondary Outcome: Absolute hearing threshold for $PTA_{most\ affected}$, change in 3PTA at 30 days, change in 4PTA at 30 days, speech understanding, partial and complete improvement in hearing, change in communication competence, quality of life, recommendation for hearing aid or cochlear implant, need for salvage therapy, change in tinnitus, hypertension, insulin sensitivity

**METHODS (BRIEF DESCRIPTION):**

- The study included 325 patients who suddenly developed ≥50 dB hearing loss within seven days at 46 sites in Germany.
- The sites included the otolaryngology department at academic and community hospitals, through the emergency department, and direct referral from private otolaryngologists.
- The trial included eight visits, which occurred either onsite in the outpatient facility or the inpatient setting.
- The trial was randomized using salient variables of age, sex, and baseline hearing threshold across treatment groups.
- Patients were assigned 1:1:1 to the following groups and were stratified according to baseline hearing threshold to more moderate to severe hearing loss.
    - Five days of high dose (250 mg) IV prednisolone + 10 days of oral placebo
    - Five days IV placebo + five days high dose (40 mg) oral dexamethasone + five days of oral placebo
    - The control group received five days of IV placebo + five days of oral prednisone (60 mg) followed by five days of tapering doses
- Change in pure tones average of the three most affected contiguous frequencies between 0.25 and 8 kHz and was assessed as the primary outcome using calibrated audiometers.
    - The minimally clinically important difference (MCID) is 10 dB.
- The secondary outcomes measured the absolute hearing threshold for $PTA_{most\ affected}$, change in 3PTA at 30 days, change in 4PTA at 30 days, speech understanding, partial and complete improvement in hearing, change in communication competence, quality of life, recommendation for hearing aid or cochlear implant, need for salvage therapy, change in tinnitus, hypertension, and insulin sensitivity.

**INTERVENTION (# IN THE GROUP):**

- IV prednisolone: 84
- Oral dexamethasone: 89

**COMPARISON (# IN THE GROUP):** 87

**FOLLOW-UP PERIOD:** 30 days

**RESULTS:**

Primary Outcome –

- IV prednisone did not improve hearing threshold compared to oral prednisone (mean change –6.8 dB; 95% CI, –15 to 1.4).
- Oral dexamethasone did not improve hearing threshold compared to oral prednisone (mean change –7.2 dB; 95% CI, –16 to 1.0).

Secondary Outcome –

- The secondary outcomes could not be assessed due to a lack of statistical analysis comparing IV prednisone or oral dexamethasone to oral prednisone.

**LIMITATIONS:**

- Lack of placebo control
- Secondary outcomes were analyzed on complete cases, which may have introduced selection bias.
- The small sample size and the choice of outcome parameters may have affected the study's power and generalizability.
- No statistical analysis was conducted for the secondary outcomes, making it difficult to determine significance.

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# New Prospects in Treating Alcohol Use Disorder

**Semaglutide and Tirzepatide Reduce Alcohol Consumption in Individuals with Obesity**

Quddos F, Hubshman Z, Tegge A, et al. Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep*. 2023;13(1):20998. Published 2023 Nov 28. doi:10.1038/s41598-023-48267-2



**KEY TAKEAWAY:** Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypetide (GIP) agonists show potential as pharmacotherapy for patients with alcohol use disorder (AUD).

**STUDY DESIGN:** Machine-learning based attribution mapping followed by remote retrospective case-control study

**LEVEL OF EVIDENCE:**

- Attribution mapping: STEP 5
- Retrospective case-control: STEP 4

**BRIEF BACKGROUND INFORMATION:** AUD contributes significantly to global mortality. GLP-1 and GLP-1/GIP agonists are FDA-approved for managing type 2 diabetes (T2DM) and obesity. GLP-1 agonists such as semaglutide have been shown to effectively reduce alcohol consumption in animal models and one human study. GLP-1 and GIP agonists such as tirzepatide do not have existing data regarding the alteration of alcohol use, though they invoke a similar mechanism of action.

*A SPIDER framework was used over the PICO analysis to describe this qualitative study.*

**SAMPLE:** Social media posts regarding weight loss medications

**PHENOMENON OF INTEREST:** Relation of GLP-1/GIP medications to weight loss and alcohol use

**DESIGN:** Keyword search and extraction tool with data visualization

**EVALUATION:** Data clustering and visualization based on recurrent themes

**RESEARCH TYPE:** Qualitative

**PATIENTS:** Obese patients who consume alcohol

**INTERVENTION:** Tirzeptide, semaglutide

**CONTROL:** No medication to manage diabetes or weight loss

**PRIMARY OUTCOME:** Alcohol consumption

**METHODS (BRIEF DESCRIPTION):**

- Two studies were conducted, including a machine learning-based attribution mapping of social media posts regarding GLP-1 or GLP-1/GIP medications followed by a remote retrospective case-control study.
- Machine-learning-based attribution mapping evaluated 68,250 Reddit posts related to GLP-1 or GLP-1/GIP agonists.
  - Posts and comments were identified using a keyword search of all approved GLP-1/GIP medications.
  - Posts were organized into eight clusters based on emotionally weighted keywords.
  - 1,580 posts referenced alcohol directly, and 72% of those addressed reduced cravings or negative effects associated with drinking.
- The remote case-control study consisted of 153 individuals recruited from social media ads.
  - The experimental group (n=106) included patients currently taking tirzepatide (n=50) or semaglutide (n=56)
  - The control group (n=47) were not on weight loss or diabetic medications
  - Participants ≥21 years old with a BMI ≥30, history of alcohol consumption, and medication use of >30 days for the intervention group were included in the study.
  - Demographics included mostly White (88%) females (81%) with a mean age of 41 years old and a mean education of 15 years.
  - Medication doses were tracked but did not play a statistically significant role in the outcomes.
  - The experimental group was given original and adapted forms of validated assessment tools to assess current and pre-medication alcohol use.
    - The Timeline Follow-Back (TLFB) is a calendar-format questionnaire to quantify alcohol use over a given time.
    - The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item scale that measures alcohol consumption behaviors.
    - The Biphasic Alcohol Effects Scale (BAES) is a 14-item scale that evaluates feelings and emotions after alcohol use.

- The control group received original forms of these assessment tools and were evaluated regarding only the current time point.
- Data from the assessment tools described above were used to compare the two groups.
- Outcomes are presented and compared using B values, which represent a regression coefficient between the independent and dependent variables.
- Analysis of Variance was used to analyze the data.

**INTERVENTION (# IN THE GROUP):** 106
**COMPARISON (# IN THE GROUP):** 47

**FOLLOW-UP PERIOD:** No follow-up

**RESULTS:**

Primary Outcome –

- Obese individuals on GLP-1/GIP agonist therapy had significantly fewer drinks per episode than their unmedicated counterparts.
  - Tirzepatide (B −1.5, standard error [SE] 0.31; *p*<.001)
  - Semaglutide (B −1.3, SE 0.30; *p*<.001)

Secondary Outcome –

- There was a reduction in binge drinking episodes between medication groups and the control group.
  - Tirzepatide (B −3.8, SE 0.68; *p*<.001)
  - Semaglutide (B − 2.1, SE 0.60; *p*<.001)
- Both tirzepatide and semaglutide demonstrated GLP-1/GIP agonist use decreased the stimulatory and sedative effects of alcohol use measured via BAES.
  - Stimulative (B −9.1, SE 1.6; *p*<.001)
  - Sedative (B −9.7, SE 1.8; *p*<.001)

**LIMITATIONS:**

- Social media analysis concedes that people with extreme response to therapy, positive or negative, are more likely to comment in the social media space, demonstrating selection bias.
- The remote study relied on retrospective surveys, which can be susceptible to recall bias.
- Remote study demographics leaned heavily toward White middle-aged females, making the results less generalizable to other groups.
- Only obese patients were included due to the current on-label use of GLP-1 medications.
- Patients who start medication for weight loss may be seeking to improve their health generally. The desire for better health alone may have increased motivation to reduce alcohol consumption.
- The average time on medication was not reported.
- Data collection spanned the COVID-19 epidemic and lockdown period, which may have independently affected alcohol use.

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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 US Government.*