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Tirzepatide's Promise in Fighting Diabetes and Obesity: Results That Last or Just a Phase?

Tirzepatide for Obesity Treatment and Diabetes Prevention

Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for Obesity Treatment and Diabetes Prevention. *N Engl J Med*. 2025;392(10):958-971. doi:10.1056/NEJMoa2410819

KEY TAKEAWAY: Tirzepatide improves weight loss and reduces the risk of developing type 2 diabetes mellitus (T2DM) in adults with obesity and prediabetes during long term treatment. However, these benefits diminish after discontinuing therapy.

STUDY DESIGN: Double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of intention to treat analysis, high drop-out rate, and potential conflict of interest due to corporate sponsorship)

BRIEF BACKGROUND INFORMATION: Nearly 1 billion people are living with obesity globally with approximately two-thirds having prediabetes, disposing them to many adverse health consequences including micro and macrovascular complications. Meaningful sustained weight loss can improve insulin resistance, leading to improved metabolic effects. Prior studies have assessed the use of tirzepatide in obesity and type 2 diabetes prevention but did not assess these factors long term. This study aimed to investigate the effects of tirzepatide on weight loss and incident T2DM in adults with obesity and prediabetes.

PATIENTS: Adults with obesity and prediabetes

INTERVENTION: Tirzepatide

CONTROL: Placebo

PRIMARY OUTCOME: Percent change in body weight, development of T2DM, and adverse events

METHODS (BRIEF DESCRIPTION):

- The study was based on secondary outcome analysis of a previously performed double-blind, randomized placebo-controlled trial.
- Study participants with a body mass index (BMI) of 30 kg/m^2 or 27 kg/m^2 with at least one obesity-related complication and prediabetes as established by the American Diabetes Association criteria were included in the study.
- Demographics were similar across treatment groups, and consisted of 60% females, 40% males, 47–49 years old, and 70% were White.
- Individuals with diabetes were excluded from the study.
- Participants were randomly assigned 1:1:1:1 ratio to receive tirzepatide (5 mg, 10 mg, 15 mg once weekly injection) or placebo for 176 weeks, with all receiving lifestyle intervention counseling.
- At various timepoints, researchers assessed glycosylated hemoglobin, fasting serum glucose, two-hour glucose tolerance test, and weight (at baseline, periodically throughout the study, and following 17 weeks off treatment).
- Participant data underwent per-protocol analysis rather than intention-to-treat analysis.

INTERVENTION (# IN THE GROUP):

- Tirzepatide 5 mg: 247
- Tirzepatide 10 mg: 262
- Tirzepatide 15 mg: 253

COMPARISON (# IN THE GROUP): 270

FOLLOW-UP PERIOD: 176 weeks of treatment followed by 17 weeks off treatment

RESULTS:

Primary Outcome –

- Tirzepatide demonstrated a dose-dependent reduction in weight compared to placebo at 176 weeks. This effect was reduced after 17 weeks off treatment.
  - 5 mg tirzepatide (mean weight reduction –12%; 95% CI, –15 to –10)
  - 10 mg tirzepatide (mean weight reduction –19%; 95% CI, –24 to –13)
  - 15 mg tirzepatide (mean weight reduction –20%; 95% CI, –22 to –17)
- Tirzepatide reduced the risk of T2DM development compared to placebo at 176 weeks (hazard ratio [HR] 0.07; 95% CI, 0.0–0.1).
- After 17 weeks off treatment tirzepatide slightly increased, although still overall reduced, the risk of T2DM development compared to placebo (HR 0.12; 95% CI, 0.1–0.2).
- Adverse event rates appear higher in the treatment groups than the placebo group based on a higher

percentage of treatment dropouts due to adverse events (as opposed to withdrawal or lost to follow up).

LIMITATIONS:

- There is a potential risk of bias because of the manufacturer of tirzepatide funded phase three of the study.
- The placebo group had a higher attrition rate than the control group, but the drop-out rate was high in all groups.
- This study used a duration follow up of 17 weeks, which may be considered short given that regression of benefits was noticed after 17 weeks.
- No intention-to-treat analysis was performed, and participant data were analyzed based on the treatment received.

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Expect the Same from Expectant Management: Retained Products of Conception after Medical Termination of Pregnancy

Expectant vs Medical Management for Retained Products of Conception after Medical Termination of Pregnancy: A Randomized Controlled Study

Tzur Y, Berkovitz-Shperling R, Goitein Inbar T, et al. Expectant vs medical management for retained products of conception after medical termination of pregnancy: a randomized controlled study. *Am J Obstet Gynecol*. 2022;227(4):599.e1-599.e9. doi:10.1016/j.ajog.2022.06.025

KEY TAKEAWAY: Medical management of retained products of conception (RPOC) after first trimester medical termination of pregnancy does not increase treatment success compared to expectant management.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Rates of medical first trimester pregnancy termination are increasing in the United States. A common complication of medical management of pregnancy termination is RPOC. However, there is limited data to inform clinical decision-making and guidelines for optimal management of this complication. This study aimed to determine if medical management of RPOC increases treatment success compared to expectant management.

PATIENTS: Women with suspected RPOC

INTERVENTION: Medical management

CONTROL: Expectant management

PRIMARY OUTCOME: Successful treatment defined as no need for surgical intervention

Secondary Outcome: Need for emergent surgical intervention, unscheduled emergency department (ED) visit, adverse side effects, pain level

METHODS (BRIEF DESCRIPTION):

- Individuals who underwent first-trimester medical termination of pregnancy at gestational age <63 days and had sonographic suspicion of RPO (intrauterine remnant >12 mm but <40 mm with positive Doppler flow) at routine three week follow up visit were included in the study.
- Individuals <18 years old with a sonographic remnant of >12 mm in thickness without a positive doppler flow, individuals with a sonographic remnant of <12 mm or >40mm, and individuals who required urgent intervention because of infection or heavy bleeding were not included in the study.
- Participants were randomized to either medical management (receiving 800 µg sublingual misoprostol) or expectant management.
- Participants and treating physicians were not blinded to their treatment group assignment.
- All participants underwent repeat ultrasound every two weeks. If RPOC persisted after two follow up visits (four weeks after diagnosis of RPOC), operative hysteroscopy was performed.
- The primary endpoint was successful treatment, defined as no need for surgical intervention for persistent RPOC within eight weeks of pregnancy termination.
- The secondary outcomes were need for emergent surgical intervention for uncontrolled bleeding or suspected uterine infection, unscheduled emergency department visits, self-reported adverse side effects (fever, chills, vomiting, nausea, and malaise), and pain level.
- Outcomes were compared between groups using relative risk with 95% confidence intervals.

INTERVENTION (# IN THE GROUP): 68

COMPARISON (# IN THE GROUP): 63

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- Medical management of RPOC after medical termination of pregnancy was not superior to expectant management (relative risk [RR] 1.1; 95% CI, 0.74–1.7).

Secondary Outcome –

- Medical management of RPOC after termination of pregnancy did not improve rates of emergent surgical intervention, unscheduled emergency department visits, self-reported adverse side effects, and pain level compared to expectant management.

LIMITATIONS:

- Study was not blinded
- Small sample size limited statistical power
- The single center setting at tertiary institutions may have limited generalizability to other populations or

institutions, especially if there was variation in diagnostic criteria for RPOC.

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Can Mirtazapine Help Your Elderly Patients Get to Sleep and Stay Asleep?

Mirtazapine for Chronic Insomnia in Older Adults: A Randomized Double-Blind Placebo-Controlled Trial the MIRAGE Study

Nguyen PV, Dang-Vu TT, Forest G, et al. Mirtazapine for chronic insomnia in older adults: a randomized double-blind placebo-controlled trial-the MIRAGE study. *Age Ageing.* 2025;54(3):afaf050. doi:10.1093/ageing/afaf050

KEY TAKEAWAY: Mirtazapine 7.5 mg daily improves chronic insomnia symptoms in elderly patients compared to placebo.

STUDY DESIGN: Randomized double-blind placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size, short follow up, and high dropout rate)

BRIEF BACKGROUND INFORMATION: Insomnia is a prevalent problem in primary care, especially in elderly patients. Cognitive behavioral therapy for insomnia (CBT-I) may not be feasible or accessible for older patients, and there are limited safe medications to use in this population. Prior studies have not included patients with chronic insomnia. This study aimed to assess the efficacy and safety of mirtazapine for chronic insomnia in older adults.

PATIENTS: Elderly patients with chronic insomnia

INTERVENTION: Mirtazapine

CONTROL: Placebo

PRIMARY OUTCOME: Chronic insomnia severity

Secondary Outcome: Sleep quality, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients were recruited via presentations, pharmacy ads, and magazines targeted at elderly people in Canada.
- Patients ≥65 years old with chronic insomnia by the International Classification of Sleep Disorders, 3rd edition (ICSD) were included in the study.
- Participants had to report difficulty initiating or maintaining sleep along with daytime symptoms at least three nights per week for at least three months.
    - Mean age was 72 years old and 60% were female.
- Patients with current use of any hypnotic drug, psychostimulant drugs, melatonin, past/current participation in CBT-I, glaucoma, or severe sleep apnea were excluded from the study.
- Participants were randomized 1:1 to mirtazapine or placebo.
- Participants and researchers were blinded to treatment group assignment
- Baseline sleep was assessed via Insomnia Severity Index (ISI). Scores range from 0–28 with a score of >15 indicating clinical insomnia, and higher score indicating higher severity of insomnia.
    - Minimally important difference (MID): 6
    - An absolute ISI score below <8 is considered remission of insomnia.
- The Pittsburgh Sleep Quality Index (PSQI) was also used to assess baseline sleep. Scores range from 0–21 with higher score indicating poorer sleep quality.
    - PSQI does not have an MID but higher scores indicate more significant sleep disturbance.
- During weeks 2–4, participants were started on 7.5 mg mirtazapine or placebo by mouth nightly for 28 days, with weekly phone visits to check for adverse events.
- Adverse events were assessed including daytime drowsiness, dry mouth, and flu-like symptoms.
- During week five, on day 36, participants had a phone visit to re-evaluate insomnia severity via ISI and PSQI
- The mean difference in ISI and PSQI was calculated, ISI mean score change was calculated using a modified intent-to-treat analysis.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 30

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- Mirtazapine improved insomnia compared to placebo based on the ISI scores (mean difference [MD] −6.5 vs −2.9, respectively; *p*=.003)
- More patients in the mirtazapine group achieved remission of their chronic insomnia after treatment compared to the placebo group (50% vs 21%, respectively; *p*=.038).

Secondary Outcome –

- There was no statistically significant difference in sleep quality measured via change in PSQI.
- Adverse events were more common in the mirtazapine group compared to placebo:
  - Daytime drowsiness (70% vs 50%)
  - Dry mouth (44% vs 40%)
  - Flu-like symptoms (41% vs 10%)
- 79% of those taking mirtazapine were affected by AEs as listed above. Six participants taking mirtazapine discontinued use due to adverse events.
- No severe adverse events or death were experienced by any participants.

LIMITATIONS:

- Relatively high dropout rate/loss to follow up
- Short-term follow-up
- Small sample-size
- Only a single low dose of mirtazapine was studied; the effects of higher doses are not known.

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Like Peanut Butter and Jelly: Iron with Probiotics Better Together

Improved Gastrointestinal Tolerance and Iron Status via Probiotic Use in Iron Deficiency Anemia Patients Initiating Oral Iron Replacement: a Randomized Controlled Trial

Koker G, Sahinturk Y, Ozcelik Koker G, et al. Improved gastrointestinal tolerance and iron status via probiotic use in iron deficiency anaemia patients initiating oral iron replacement: a randomised controlled trial. *Br J Nutr*. 2024;132(10):1308-1316. doi:10.1017/S0007114524002757

KEY TAKEAWAY: Oral iron therapy with added *Lactobacillus plantarum* 299v significantly improves gastrointestinal (GI) tolerance and enhances iron status markers, leading to better treatment adherence and outcomes.

STUDY DESIGN: Prospective, randomized, controlled, non-placebo trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Iron deficiency anemia (IDA) is one of the most common micronutrient deficiencies worldwide and is typically treated with oral iron supplementation. However, GI side effects such as nausea, constipation, abdominal pain frequently limit adherence to therapy. Emerging evidence suggests that probiotics, particularly *Lactobacillus plantarum* 299v, may enhance iron absorption and reduce GI intolerance, but data in IDA populations remains limited. This study aimed to evaluate whether adding L. plantarum 299v to oral iron therapy improves GI tolerability and iron status in patients with newly diagnosed IDA.

PATIENTS: Adults with IDA

INTERVENTION: Oral iron replacement therapy (IRT) plus *Lactobacillus plantarum* 299v probiotic supplementation (IRT-Pro)

CONTROL: Oral IRT alone

PRIMARY OUTCOME: GI intolerance and treatment discontinuation

Secondary Outcome: Hemoglobin levels, serum iron, ferritin, transferrin saturation, and total iron-binding capacity (TIBC)

METHODS (BRIEF DESCRIPTION):

- Patients at least 18 years old with newly diagnosed IDA were recruited from a tertiary internal medicine clinic in Turkey between September 2020 and March 2022.
- Diagnosis of IDA was based on ferritin <20 ng/mL or transferrin saturation <15%, with hemoglobin levels <12 g/dL.
- 96% of the 295 enrolled participants were female, with a mean age of 36 years old.
- Patients with prior iron therapy, GI conditions (e.g., IBS, IBD, celiac disease), untreated menometrorrhagia or hemorrhoids, or other chronic illnesses were excluded from the study.
- Patients were randomized 1:1 to receive either:
  - Oral 100 mg elemental iron (ferrous fumarate) once daily for three months.
  - Same iron regimen plus *Lactobacillus plantarum* 299v probiotic (10 billion CFU/day) for the first 30 days of therapy.
- Randomization was performed using a computer-generated sequence.
- GI intolerance symptoms (i.e. nausea, vomiting, abdominal pain, diarrhea, bloating, constipation, loss of appetite) were assessed using a seven-item binary questionnaire based on the Gastrointestinal Symptom Rating Scale (GSRS) and the Appetite and Dietary Assessment Tool.
- Treatment discontinuation was defined as cessation of iron therapy, particularly within the first 30 days.
- Hemoglobin (Hb) levels and serum iron markers were measured at baseline and three months using standard laboratory analyzers:
  - Ferritin (ng/mL)
  - Serum iron (µg/dL)
  - Total iron-binding capacity (TIBC, µg/dL)
  - Transferrin saturation (%)
- Changes from baseline values were calculated to assess treatment response.

INTERVENTION (# IN THE GROUP): 138

COMPARISON (# IN THE GROUP): 157

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- IRT-Pro significantly reduced gastrointestinal intolerance symptoms compared to iron therapy alone (13% vs. 47%; p<.001).

- IRT-Pro lowered the rate of treatment discontinuation in patients within the first 30 days compared to iron therapy alone (3.6% vs 16%; *p*<.001).

Secondary Outcome –

- IRT-Pro improved serum hemoglobin levels more than iron therapy alone (median change 0.9 g/dL vs 0.4 g/dL; *p*<.001).
- IRT-Pro increased serum iron levels more than iron therapy alone (median change 24 µg/dL vs 8.0 µg/dL; *p*<.001).
- IRT-Pro improved transferrin saturation more than iron therapy alone (median change 8.2% vs 2.1%; *p*<.001).
- IRT-Pro increased ferritin levels more than iron therapy alone (median change 13 ng/mL vs 5.0 ng/mL; *p*<.001).
- IRT-Pro reduced TIBC more than iron therapy alone (median change –46 µg/dL vs –11 µg/dL; *p*<.001).

LIMITATIONS:

- The study lacked a placebo control, which increased the risk of bias for subjective outcomes like gastrointestinal symptoms.
- The trial was unblinded, potentially introducing expectation bias from both participants and researchers.
- The sample was predominantly female (96%), limiting generalizability.
- Symptom assessments relied on self-reported, binary data without capturing severity or frequency, reducing the granularity of the findings.

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