GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 49

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of December 4 - 8, 2023

SPOTLIGHT: Does Once Weekly Insulin Allow for Fewer Injections and Better Results?

- Does Exercise Help Prevent the Progression of Mild Cognitive Impairment?
- Resistant Depression: To Add or To Change?
- Can Nuts Prevent Alzheimer's?
- Turning the Tide on Diabetes: Tirzepatide Surpasses Semaglutide

Does Once Weekly Insulin Allow for Fewer Injections and Better Results?

Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults with Insulin-Naïve Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial

Lingvay I, Asong M, Desouza C, et al. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults with Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. *JAMA*. 2023;330(3):228-237. doi:10.1001/jama.2023.11313

KEY TAKEAWAY: Once-weekly insulin icodec was significantly better at lowering hemoglobin A1c (HbA1c) than once-daily degludec with minimal increase in risk for hypoglycemic events. Weekly insulin use could greatly reduce the number of injections patients with insulin-dependent diabetes require in a year.

STUDY DESIGN: Randomized, double-masked, noninferiority, treat-to-target, phase 3a clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: With the progression of type 2 diabetes, many patients need initiation of insulin for improved glycemic control. Insulin icodec has been shown to have a long half-life of approximately one week and has similar safety and efficacy when compared to once-daily insulin glargine; however, icodec has not been compared to daily basal insulin in insulin-naïve patients. Weekly icodec could improve compliance in patients with insulin-dependent type 2 diabetes by reducing the number of injections from at least 365 per year to as low as 52 per year.

PATIENTS: Adults with insulin-naïve type 2 diabetes

INTERVENTION: Once-weekly insulin icodec

CONTROL: Once-daily insulin degludec

PRIMARY OUTCOME: Change in HbA1c

Secondary Outcome: Change in fasting glucose, mean weekly insulin dose, change in body weight, number of hypoglycemic episodes

METHODS (BRIEF DESCRIPTION):

- Participants were adults with insulin-naïve type 2 diabetes with an HbA1c of 7.0% to 11.0%.
- The intervention group received once-weekly icodec and once-daily placebo.
- The control group received once-daily degludec and once-weekly placebo.
- Medication dosages were adjusted every week with a fasting blood glucose goal of 80–130 mg/dL.
- The primary outcome was the change in HbA1c from baseline to week 26. The study included all randomized participants regardless of trial treatment adherence or changes in noninsulin medications.
- Secondary outcomes included change in laboratory-assessed fasting glucose from baseline to week 26, mean total weekly insulin dose in the last two weeks of treatment, change in body weight during the study, and the number of level two (blood glucose <54 mg/dL) and/or level three (hypoglycemia with severe cognitive impairment requiring external assistance) hypoglycemic events.

INTERVENTION (# IN THE GROUP): 294

COMPARISON (# IN THE GROUP): 294

FOLLOW-UP PERIOD: 26-week treatment period and a five-week follow-up period.

RESULTS:

Primary Outcome –

- HbA1c decreased from 8.6% to 7.0% in the intervention group and from 8.5% to 7.2% in the control group (estimated treatment difference [ETD] –0.2%; 95% CI, –0.3% to –0.1%), making once-weekly icodec non-inferior and superior to once-daily degludec.

Secondary Outcome –

- The change in mean fasting plasma glucose was the same in each group at –54 mg/dL (ETD 0 mg/dL; 95% CI, –6 to 6).
- The difference in mean weekly insulin between treatment groups during the last two weeks of treatment was not statistically significant (estimated treatment ratio 1.10; 95% CI, 0.98–1.22).
- The change in body weight from baseline to week 26 was also not statistically significant (ETD 0.46 kg; 95% CI, –0.19 to 1.10).
- From baseline to week 26, there was a statistically significant difference in level two or three hypoglycemic events with 0.35 events per patient-year in the icodec group and 0.12 events per patient-year in the degludec group (ERR 3.12; 95% CI, 1.30–7.51).

LIMITATIONS:

- Sustained effects of treatment were not studied as the trial only had a 26-week treatment period.
- A higher percentage of patients in the icodec group were on a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist which could have improved glycemic control compared to the degludec group.
- To be included in the study, participants' BMI had to be less than or equal to 40.0 kg/m^2; thus, results may not apply to patients with class III obesity.

Taylor Apley, MD
Texas A&M FMR
Bryan, TX

Does Exercise Help Prevent the Progression of Mild Cognitive Impairment?

Effects of Exercise Alone or Combined with Cognitive Training and Vitamin D Supplementation to Improve Cognition in Adults with Mild Cognitive Impairment: A Randomized Clinical Trial

Montero-Odasso M, Zou G, Speechley M, et al. Effects of Exercise Alone or Combined With Cognitive Training and Vitamin D Supplementation to Improve Cognition in Adults With Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA Netw Open.* 2023;6(7):e2324465. Published 2023 Jul 3. doi:10.1001/jamanetworkopen.2023.24465

KEY TAKEAWAY: Exercise and cognitive training are possibly beneficial in preventing cognitive impairment from worsening into dementia.

STUDY DESIGN: Multisite, double-blinded, fractional factorial randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current studies demonstrate that individual exercise, cognitive training, and vitamin D supplementation can improve cognition in older adults. There are very few studies that included cognitively impaired populations. This study investigates a multimodal approach to improve cognition among patients with mild impairment.

PATIENTS: Older adults with mild cognitive impairment

INTERVENTION: Exercise, cognitive training, vitamin D

CONTROL: Sham activities and placebo

PRIMARY OUTCOME: Cognitive function

Secondary Outcome: Cognition at 12 months

METHODS (BRIEF DESCRIPTION):

- Patients 60–85 years old with mild cognitive impairment were recruited from communities surrounding five Canadian academic institutions.
- Inclusion criteria were objective cognitive impairment in memory, executive function, attention and/or language, preserved activities of daily living, and absence of dementia.
- Exclusion criteria were patients with major mental health illnesses and those already participating in exercise programs or taking vitamin D.
- The mean age was 73.1 years old, 49.1% were female (N=86), and an average MOCA of 22.6.
- The treatment group received aerobic and resistance exercise training three times a week for 20 weeks for the exercise intervention.
  - The control group received stretching, balancing, and toning exercises at the same frequency and duration.
- The treatment group received tablet-based visuomotor tasks targeting memory and attention for the cognition intervention.
  - The control group received tablet-based touristic search and video watching.
- The treatment group received vitamin D 10,000 IU three times per week for the vitamin D intervention.
  - The control group received a matching placebo.
- The fractional design of the study included five groups:
  - Group 1 received exercise, cognition training, and vitamin D.
  - Group 2 received exercise, cognition training, and a placebo of vitamin D.
  - Group 3 received exercise, sham cognition training, and vitamin D.
  - Group 4 received exercise, sham cognition training, and a placebo of vitamin D.
  - Group 5 received sham exercise, sham cognition training, and a placebo of vitamin D.
- Cognitive function was measured via the Alzheimer Disease Assessment Scale-Cognitive (ADAS Cog 13) scaled 0–85 with higher scores indicating more cognitive impairment and the plus variant which included five additional tests.
- Cognition was measured at zero, six, and 12 months.

INTERVENTION (# IN THE GROUP):

- Group 1: 31
- Group 2: 28
- Group 3: 31
- Group 4: 28

COMPARISON (# IN THE GROUP): Group 5: 26

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Patients receiving aerobic exercise had improved cognition as compared to balance toning exercises

(mean difference [MD] –1.79; 95% CI, –3.27 to –0.31).

- Patients receiving cognitive training and aerobic exercise improved over those with exercise alone (MD –1.4; 95% CI, –2.7 to –0.21).
- There was no difference in cognition among those who received vitamin D versus placebo (MD 0.35; 95% CI, –0.93 to 1.62).
- At 12 months, all groups had a trend toward cognitive improvement, however, none were statistically significant.
- There was no change in any groups regarding executive function as measured by ADAS-Cog Plus including all domains vs control (MD –0.09; 95% CI, –0.29 to 0.11).

LIMITATIONS:

- This study was limited by a small number of participants.
- Although results are statistically significant there is questionable clinical significance due to the broad range in the ADAS scale.
- Participants were masked such as with exercise intervention but may have been able to identify if receiving sham or intervention.

Eline Cove, DO
Alaska Family Medicine Residency
Anchorage, AK

Resistant Depression: To Add or To Change?

Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression

Lenze EJ, Mulsant BH, Roose SP, et al. Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression. *N Engl J Med*. 2023;388(12):1067-1079. doi:10.1056/NEJMoa2204462

KEY TAKEAWAY: Both augmentation and switch of antidepressants can improve well-being in treatment-resistant geriatric depression.

STUDY DESIGN: Unblinded randomized two-step trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of participant blinding)

BRIEF BACKGROUND INFORMATION: Separate studies on treatment-resistant depression have demonstrated that augmentation with or switching to bupropion and augmentation with aripiprazole have been effective in reducing depression. One prior study suggested that augmentation with aripiprazole or bupropion was more effective than switching medications. This study investigates both the benefits and risks of augmentation compared to switching medications in geriatric treatment-resistant depression.

PATIENTS: Older adults with treatment-resistant depression

INTERVENTION: Step 1: Augmentation with aripiprazole or bupropion or switch to bupropion; Step 2: Augmentation with lithium or switch to nortriptyline for non-responders

CONTROL: Baseline and between-group differences

PRIMARY OUTCOME: Psychological well-being

Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Adults 60 years old and older with treatment-resistant depression were recruited from five university sites through referrals from primary physicians, psychiatrists, advertisements, and automated alerts in electronic medical records.
- Patients were included if they had lack of remission of depression after two or more trials of antidepressants and a patient health questionnaire (PHQ) score >9.
    - Patients were excluded if they had a high risk of suicide, a lifetime diagnosis of bipolar disorder, or clinically significant hearing impairment.
    - The mean age was 69 years old with 68% women and 32% men, the baseline PHQ-9 score was 15–16, and the onset age of depression was 30–35 years old.
- Initially, groups were randomized to augmentation with oral aripiprazole (AA) starting at 2.5 mg/day and increasing to a maximum of 15 mg/day, augmentation with oral bupropion (BA) starting with 150 mg/day and increasing to a target of 300 mg/day with a maximum of 450 mg/day, or a switch to bupropion (BS) at the same dose for 10 weeks.
- Step 2 included patients who could not participate in Step 1 due to previous trials of bupropion or aripiprazole and those who did not have improvement with the initial intervention.
    - Patients received augmentation with oral lithium (LA) starting at 150 or 300 mg/day with 0.6 mmol/L as the goal for serum levels, or a switch to nortriptyline (NS) starting at 25 mg/day increasing to 1 mg/kg with serum level target 80–120 ng/mL.
- Psychological well-being was measured with the NIH toolbox positive affect and general life satisfaction subscales of affect and satisfaction (normative population mean T score of 50; higher scores indicating greater well-being) at a 10-week follow-up.
- Safety Outcomes: Falls were measured via phone interviews with a fall defined as any “slip or trip in which you lost your balance and landed on the floor or ground or lower level”.

INTERVENTION (# IN THE GROUP):

- Step 1:
    - AA: 211
    - BA: 206
    - BS: 202
- Step 2:
    - LA: 127
    - NS: 121

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 10 weeks

RESULTS:

Primary Outcome –

- Step 1:
  - All groups had an improvement in well-being scores as measured by the change in T score at 10 weeks:
    - AA: 4.83 (95% CI, 3.28–6.38)
    - BA: 4.33 (95% CI, 3.76–5.91)
    - BS: 2.04 (95% CI, 0.43–3.66)
  - AA resulted in greater improvement in affect and life satisfaction compared to BS (MD 2.79; 95% CI, 0.56–5.02).
  - There was no difference between BA and BS in well-being scores (MD 2.29; 95% CI, 01–4.57).
  - AA did not improve affect and life satisfaction compared to BA (MD 0.5; 95% CI, –1.69 to 2.69).
- Step 2:
  - There was no difference in affect and life satisfaction between LA and NS (MD 0.99; 95% CI, –1.92 to 3.91).
- Safety Outcomes: Falls were considered decreased in AA vs BA (risk ratio [RR] 0.59; 95% CI, 0.38–0.92) but were similar among all other group comparisons.

LIMITATIONS:

- The study lacked a control group to evaluate placebo effect.
- The cost associated with medication change was on the patient if insurance did not cover it.
- The study had a predominately White, homogenous population.
- The exclusion criteria may have selected patients with higher levels of depression given suicidality and sensory loss.

Jaclyn Long, MD
Alaska Family Medicine Residency
Anchorage, AK

Can Nuts Prevent Alzheimer's?

Trial of the MIND Diet for Prevention of Cognitive Decline in Older Persons

Barnes LL, Dhana K, Liu X, et al. Trial of the MIND Diet for Prevention of Cognitive Decline in Older Persons. *N Engl J Med.* 2023;389(7):602-611.
doi:10.1056/NEJMoa2302368

KEY TAKEAWAY: There was no measurable difference in cognitive improvement with the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet compared with a calorie-restricted diet.

STUDY DESIGN: Two-site randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to non-blinded participants)

BRIEF BACKGROUND INFORMATION: Prior studies on diet have investigated the effects of the DASH and Mediterranean diet on cardiovascular disease. However, these studies have not looked specifically at the effect on brain health or cognition. There has been limited investigation surrounding specific foods or the role of a diet in a decreased risk of dementia.

PATIENTS: Adults with cognitive impairment

INTERVENTION: MIND diet

CONTROL: Caloric restriction

PRIMARY OUTCOME: Improvement in cognitive scores

Secondary Outcome: Change from baseline in MRI, adverse events

METHODS (BRIEF DESCRIPTION):

- Adults ≥ 65 years old with a family history of Alzheimer's were recruited from two sites in Chicago and Boston.
- Inclusion criteria were MOCA score of 22/30 or greater, overweight status, and a suboptimal diet.
- Exclusion criteria were Alzheimer's disease, psychiatric medication use, food allergies, a history of substance abuse in the last six months, and recent cardiovascular disease or event.
- Participants' mean age was 70.4 years old, approximately 35% male, majority White, with an average of 17 years of education in both groups and apolipoprotein E carrier status of 25.2% in the MIND diet and 32.3% in control.
- Dietary counseling led by registered dieticians occurred weekly for the first six months of the trial, every other week for the next six months, and twice monthly thereafter.
- MIND diet participants received education on foods to consume, behavioral strategies to lose weight, and received monthly supplies of blueberries, mixed nuts, and extra virgin olive oil.
    - The comparison or caloric restriction group received portion control counseling by dieticians focused on calorie tracking and a monthly $30 gift card.
- Baseline cognition was measured via a global composite score using 12 publicly available cognition tests; a higher score indicating better cognitive performance.
- Cognition testing was done at six, 12, 24, and 36 months.
- MRI changes were measured via intracranial volume measurements of total, hippocampal, and white matter lesions at baseline and year three follow-up.

INTERVENTION (# IN THE GROUP): 301

COMPARISON (# IN THE GROUP): 303

FOLLOW-UP PERIOD: 36 months

RESULTS:

Primary Outcome –

- The MIND diet group had a similar change in global cognition scores as compared to the caloric restriction group from baseline to three years (mean difference [MD] 0.035; 95% CI, –0.022 to 0.092).

Secondary Outcome –

- Changes in MRI were similar between the MIND diet and calorie restriction groups regarding white matter, hippocampal volume, and total grey and white matter volume.
- Weight loss was similar for both groups (MIND diet –5 kg vs. control diet –4.8 kg).
- Cardiovascular events were numerically higher in the control diet (MIND diet 17 events vs. 32 events in the control diet group).

LIMITATIONS:

- This study was not blinded to participants.
- This study included a well-educated, older population of mostly European descent which may not be generalizable to the general population.

- This study would be difficult to reproduce in the community with dietary education and provided food supplies.
- There was a high dropout rate in the MIND group.

Carolyn Stordeur, MD
Alaska Family Medicine Residency
Anchorage, AK

Turning the Tide on Diabetes: Tirzepatide Surpasses Semaglutide

Tirzepatide vs Semaglutide Once Weekly in Patients with Type 2 Diabetes

Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021;385(6):503-515. doi:10.1056/NEJMoa2107519

KEY TAKEAWAY: Tirzepatide offers a greater reduction in glycated hemoglobin (HbA1c) and weight than semaglutide as a once-weekly adjunctive treatment in adults with type 2 diabetes mellitus (DM) sub-optimally controlled with metformin monotherapy.

STUDY DESIGN: Randomized parallel group unblinded trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to disease-oriented primary outcome)

BRIEF BACKGROUND INFORMATION: Glucose-dependent insulinotropic polypeptide (GIP) is an incretin that can be insulinotropic or glucacogonotropic, enhances insulin sensitivity, and may also enhance the peripheral action of glucagon-like peptide-1 (GLP-1). Tirzepatide is a novel dual GIP/GLP-1 receptor agonist that may have greater long-term effects in diabetes and obesity than a GLP-1 receptor agonist alone. This study compares low (5 mg), medium (10 mg), and high (15 mg) doses of tirzepatide to a moderate (1 mg) dose of semaglutide.

PATIENTS: Adults with type 2 DM

INTERVENTION: Tirzepatide at various doses

CONTROL: Semaglutide

PRIMARY OUTCOME: Change in HbA1c

Secondary Outcomes: Changes in body weight, changes in lipid profile, adverse events

METHODS (BRIEF DESCRIPTION):

- This was an industry-sponsored randomized, non-blinded trial.
- A total of 1,878 eligible patients were randomized in a 1:1:1:1 ratio to receive either once-weekly semaglutide 1 mg, or tirzepatide 5 mg, 10 mg, or 15 mg for a 40-week treatment period.
- Adults with type 2 DM on metformin (greater than 1.5 g/day) whose HbA1c ranged from 7.5% to 10.5%, and whose BMI was stable around 25 for the past three months were included in the trial.
- Exclusion criteria were type 1 DM, estimated glomerular filtration rate <45 mL/min/1.73m^2, pancreatitis, diabetic retinopathy, or maculopathy.
- Semaglutide was started at 0.25 mg weekly and titrated up to a target dose of 1 mg on week eight.
- Tirzepatide was started at 2.5 mg weekly and titrated up to one of three double-blinded target doses and then maintained.
    - Tirzepatide 5 mg was achieved at four weeks, 10 mg was achieved at 12 weeks, and 15 mg was achieved at 20 weeks.
- Doses could not be reduced.
- The primary outcome measure was the mean change in A1c at the end of the treatment period.
- The secondary outcomes were changes in body weight and lipid profiles.

INTERVENTION (# IN THE GROUP):

- Tirzepatide 5 mg: 470
- Tirzepatide 10 mg: 469
- Tirzepatide 15 mg: 470

COMPARISON (# IN THE GROUP): Semaglutide 1 mg: 469

FOLLOW-UP PERIOD: 40 weeks

RESULTS:

Primary Outcome –

- Tirzepatide demonstrated a greater reduction in A1C as compared to semaglutide at each dose:
    - Tirzepatide 5 mg vs semaglutide 1 mg –2.01% vs. –1.86% (estimated treatment difference [ETD] –0.15; 95% CI, –0.28 to –0.03)
    - Tirzepatide 10 mg vs semaglutide 1 mg –2.04% vs –1.86% (ETD –0.39%; 95% CI, –0.51 to –0.26)
    - Tirzepatide 15 mg vs semaglutide 1 mg –2.30% vs –1.86% (ETD –0.45%; 95% CI, –0.57 to –0.37)

Secondary Outcomes –

- Tirzepatide demonstrated a greater mean reduction in body weight compared to semaglutide:
    - Tirzepatide 5 mg vs semaglutide 1 mg –7.6 kg vs –5.7 kg (ETD –1.9 kg; 95% CI, –2.8 to –1.0)
    - Tirzepatide 10 mg vs semaglutide 1 mg –9.3 kg vs –5.7 kg (ETD –3.6 kg; 95% CI, –4.5 to –2.7)
    - Tirzepatide 15 mg vs semaglutide 1 mg –11.2 kg vs –5.7 kg (ETD –5.5 kg; 95% CI, –6.4 to –4.6)
- Most reported adverse events across all groups were mild to moderate nausea, diarrhea, and

emesis being the most common and with higher numbers during tirzepatide dose escalations.
- Hypoglycemia was rare but was reported more often in the tirzepatide group.
- There were 12 deaths in the tirzepatide group and one in the semaglutide group, all adjudicated as being caused by either COVID-19 or cardiovascular causes.

LIMITATIONS:

- There was no blinding between the treatment and comparator groups.
- Lower (0.5 mg) and higher doses (2 mg) of semaglutide were not used.
- Tirzepatide 15 mg reached a steady state for only 16 weeks due to a titration scheme.
- There was no disclosed cost analysis.
- The authors were employed by the industry sponsor.

Amina Faruque, MD
Northern Light Eastern Maine Medical Center FMR
Bangor, ME