GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of November 14 - 18, 2022

SPOTLIGHT: MAB to the Rescue? Reduction of Episodic Migraines with Erenumab

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- Empagliflozin: Heart Failure Outcome and Age
- Intuitive Eating for Better Glycemic Control?

MAB to the Rescue? Reduction of Episodic Migraines with Erenumab

One-Year Sustained Efficacy of Erenumab in Episodic Migraine: Results of the STRIVE Study

Goadsby PJ, Reuter U, Hallström Y, et al. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology*. 2020;95(5):e469-e479. doi:10.1212/WNL.0000000000010019

KEY TAKEAWAY: Erenumab may reduce monthly migraine days in patients with episodic migraines.
STUDY DESIGN: Randomized controlled trial (RCT)
LEVEL OF EVIDENCE: STEP 3 (downgraded because no direct statistical comparisons were performed)

BRIEF BACKGROUND INFORMATION: Up to 12% of the U.S. population suffers from migraines, which may negatively impact quality of life, interpersonal relationships, and economic productivity, but current existing treatments are not effective for all migraine patients. Erenumab is a monoclonal antibody that binds to and blocks the calcitonin gene-related peptide receptor, which is involved in migraine pathophysiology.

PATIENTS: Adults with episodic migraines
INTERVENTION: Erenumab injection 140 mg
CONTROL: Erenumab injection 70 mg
PRIMARY OUTCOME: Change from baseline in monthly migraine days (MMD)
Secondary Outcomes: Percentage of patients who experienced >50%, >75%, or 100% reduction in MMD compared to baseline, treatment emergent adverse events (TEAEs)

METHODS (BRIEF DESCRIPTION):

- Patients were included in this study after completing the initial 24 weeks of the STRIVE trial (Study to Evaluated the Efficacy and Safety of Erenumab in Migraine Prevention), during which they were randomized to placebo, 70 mg erenumab, or 140 mg erenumab IM monthly.
- At the end of 24 weeks double blind treatment phase (DBTP), participants were re-randomized to evaluate for long-term efficacy ("active treatment phase" or ATP).
- Inclusion: Patients 18–66 years old (mean 42) in North America and Europe with episodic migraine with or without aura 4–14 days per month.
- Exclusion: Lack of response with two or more preventive medications, or having medication overuse headache
- Participants received either 70 mg or 140 mg IM once monthly and were followed for 28 weeks after re-randomization (52 weeks from baseline).

INTERVENTION (# IN THE GROUP): 424
COMPARISON (# IN THE GROUP): 421

FOLLOW UP PERIOD: 52 weeks

RESULTS:

- Compared to baseline, at 52 weeks, MMD was reduced by 4.2 days in the 70 mg group and 4.6 days in the 140 mg (no statistical comparison done).
- The percentage of patients achieving >50% reduction in MMD compared to baseline was similar between groups (61% vs 65%; no statistical comparison done).
- Compared to pre-ATP baseline at 24 weeks, MMD was reduced by 1.1 days the 70 mg group and 1.8 days in the 140 mg group (no statistical comparison done).
- There were similar TEAEs (57% vs 55% for 70 mg and 140 mg doses respectively) and serious adverse events (3% vs 3%) in both groups (no statistical comparison provided).

LIMITATIONS:

- No direct statistical comparisons between the two dosage groups were presented.
- Lack of generalizability: Patient population limited to those with prior or concurrent migraine medication use. Additionally, patients who failed two or more preventive therapies or had medication overuse were excluded.
- Lack of diversity in study population: 84% were women and 90% were White, limiting generalizability.
- The study was funded by Amgen, which is a co-developer of erenumab.

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Can Methylphenidate Improve the Quality of Life in Patients with Alzheimer Disease?

Effect of Methylphenidate on Apathy in Patients with Alzheimer Disease: The ADMET 2 Randomized Clinical Trial

Mintzer J, Lanctôt KL, Scherer RW, et al; ADMET 2 Research Group. Effect of Methylphenidate on Apathy in Patients with Alzheimer Disease: The ADMET 2 Randomized Clinical Trial. *JAMA Neurol.* 2021 Nov 1;78(11):1324-1332.

KEY TAKEAWAY: Methylphenidate may have a modest but potentially clinically significant effect on apathy in patients with Alzheimer Disease.

STUDY DESIGN: Multicenter, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Two studies on catecholaminergic agents such as methylphenidate have demonstrated preliminary efficacy in apathy among patients with Alzheimer Disease (AD). This study investigates the effect over a longer duration.

PATIENTS: Adults with probable AD

INTERVENTION: Methylphenidate

CONTROL: Placebo

PRIMARY OUTCOME: Apathy and patient behavior

Secondary Outcomes: Motivation, engagement, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients were 70–81 years old from nine U.S. and one Canadian clinic specializing in dementia care met criteria for AD.
  - The mean age was 76 years old.
  - Participants had AD, mini-mental status exam (MMSE) scores between 10 and 28, and clinical apathy for at least four weeks per Neuropsychiatric Inventory (NPI).
  - Patients with current or previous major depression, agitation, delusions, frequent hallucinations, and those with changes in AD medications, antidepressants, and benzodiazepines within 30 days were excluded.
- For six months, the treatment group received 5 mg of methylphenidate twice daily for three days followed by 10 mg methylphenidate twice daily.
  - The comparison group received placebo (cellulose) tablets twice daily.
- Apathy measured via NPI Apathy Score (0 to 48, higher scores indicating more apathy) during monthly visits for six months and Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC) (scored 0 to 7, higher ratings indicating worsening apathy from baseline) at 0 and 6 months.
- Motivation and engagement were measured via Dementia Apathy Interview and Rating Scale (16 item scale informant rated scale, higher scores indicating more apathy) during monthly visits for six months.
- Monitored adverse events included hospitalization, death, and clinically significant weight loss (≥7% from baseline).

INTERVENTION (# IN THE GROUP): 89

COMPARISON (# IN THE GROUP): 92

FOLLOW UP PERIOD: Six months

RESULTS:

Primary Outcomes –

- Methylphenidate decreased apathy levels compared to placebo at six months (mean difference change –1.3; 95% CI, –2.0 to –0.47).
- Methylphenidate improved ratings of behavior compared to placebo at six months (odds ratio for mean difference change 1.4; 95% CI, 1.0–2.0).

Secondary Outcomes –

- Methylphenidate and placebo similarly improved motivation and engagement.
- Adverse event rates were similar between the methylphenidate and placebo groups except for unintentional weight loss (methylphenidate n=14 vs placebo n=8).

LIMITATIONS:

- The population was homogenous and included predominantly White adults.
- There was no biomarker for diagnosis of AD.
- The duration of effect of methylphenidate was limited to the study length of six months.
- The study contained incomplete information about patients who withdrew.

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Empagliflozin: Heart Failure Outcome and Age

Empagliflozin Improves Outcomes in Patients with Heart Failure and Preserved Ejection Fraction Irrespective of Age

Böhm M, Butler J, Filippatos G, et al. Empagliflozin Improves Outcomes in Patients with Heart Failure and Preserved Ejection Fraction Irrespective of Age. *J Am Coll Cardiol*. 2022;80(1):1-18. doi:10.1016/j.jacc.2022.04.040

KEY TAKEAWAY: Age does not significantly affect hospitalization and cardiovascular death among heart failure patients taking empagliflozin with preserved ejection fraction.

STUDY DESIGN: Double blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: It has been documented that empagliflozin reduces cardiac events in patients with heart failure and preserved ejection fraction, but it is unclear whether the benefits of empagliflozin persist with increasing age.

PATIENTS: Heart failure patients with preserved ejection fractions

INTERVENTION: Empagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Time to first heart failure hospitalization or cardiovascular death

Secondary Outcomes: Heart failure hospitalizations, change in glomerular filtration rate, clinical cardiomyopathy scores, adverse events

METHODS (BRIEF DESCRIPTION):

- This study was an intention-to-treat analysis of patients enrolled in empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) recruited from 622 institutions in 23 countries (n=5,988).
- Inclusion criteria:
  - New York Heart Association (NYHA) functional class II-IV heart failure patients with ejection fractions of more than 40%, regardless of diabetic status.
  - Elevated N-terminal pro–B-type natriuretic peptide levels (>900 pg/mL or >300 pg/mL in patients with or without atrial fibrillation [AF], respectively).
  - Evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement), or a documented heart failure hospitalization within the 12 months before enrollment.
- Patients were randomly assigned to either empagliflozin 10 mg or placebo once daily in addition to standard therapy.
- Empagliflozin and placebo groups for each of four age categories (refer to Results) were compared on the following outcomes:
  - Cardiovascular death (CVD) or 1st heart failure hospitalization (HFH)
  - Total HFH
  - Decline in estimated glomerular filtration rate (eGFR)
  - Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score (KCCQ-CSS) to assess health-related quality of life. Scores range from 0 to 100, with higher scores indicating better symptoms.
  - Frequency of adverse events

INTERVENTION (# IN THE GROUP): 2,997

COMPARISON (# IN THE GROUP): 2,991

FOLLOW UP PERIOD: Median 26 months

RESULTS:

Primary Outcomes –

- Compared to placebo, empagliflozin did not reduce HFH and CVD among patients ages <65 years old and 65–74 years old. However, empagliflozin significantly reduced HFH and CVD among patients ages 75 years and older.
  - <65 years (n=1,199; hazard ratio [HR] 0.8; 95% CI, 0.6–1.1)
  - 65–74 years (n=2,214; HR 0.9; 95% CI, 0.7–1.1)
  - 75–79 years (n=1,276; HR 0.7; 95% CI, 0.5–0.9)
  - >80 years (n=1,299; HR 0.7; 95% CI, 0.6–0.9)
- In sum, the differences across the four age groups in time to first HFH or CVD were not significant (*P* for trend =.33).

Secondary Outcomes –

- Age did not significantly influence the effect of empagliflozin on total HFH.
- Empagliflozin significantly reduced eGFR decline between weeks four and 52 (mean slope difference of eGFR decline between empagliflozin and placebo was 1.4; 95% CI, 1.1–1.7).
  - Empagliflozin attenuated the eGFR decline similarly across all age groups (*P* for trend=.32).
- Empagliflozin did not improve health-related quality of life at week 52 across all age groups at week 52 (*P* for trend=.30).

- Compared to placebo, empagliflozin was associated with a higher incidence of genital infections, an adverse event of empagliflozin.
    - 65–74 years (empagliflozin 1.0 vs placebo 0.38; *P*=.01)
    - 75–79 years (empagliflozin 2.0 vs placebo 0.44; *P*=.002)

LIMITATIONS:

- Treatment was not randomized to age groups.
- The accompanying "standard therapy" was not necessarily controlled for during the treatment course.
- The EMPEROR-Preserved trial, from which patients of this study were selected, was funded by pharmaceutical companies.

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Intuitive Eating for Better Glycemic Control?

Intuitive Eating is Associated with Glycemic Control in Type 2 Diabetes

Soares FLP, Ramos MH, Gramelisch M, et al. Intuitive eating is associated with glycemic control in type 2 diabetes. *Eat Weight Disord*. 2021;26(2):599-608. doi:10.1007/s40519-020-00894-8

KEY TAKEAWAY: Intuitive eating is associated with a lower chance of presenting to clinic with inadequate glycemic control. This relationship persisted across BMI categories.
STUDY DESIGN: Cross-sectional study
LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus (T2DM) is a chronic condition affecting 8.8% of the population worldwide. Lifestyle management is central to T2DM management with weight and food group restriction historically highlighted. Recent ADA guidelines have shifted emphasis to a more patient-centered approach considering psychological outcomes such as autonomy and pleasure associated with eating and have de-emphasized weight as a singular focus. There is an emerging body of literature evaluating intuitive eating as one method for improving metabolic outcomes, including blood pressure and cholesterol. This study aimed to establish whether there is an association between intuitive eating and glycemic control in T2DM.

PATIENTS: Adults with type 2 diabetes mellitus
INTERVENTION: High intuitive eating score
CONTROL: Low intuitive eating score
OUTCOME: Glycemic control (HbA1c <7%)

METHODS (BRIEF DESCRIPTION):

- Conducted in a university hospital endocrinology clinic in Brazil.
- 179 patients, 74% female, 54% over 60 years old
- Inclusion criteria: 20 years old or older with T2DM diagnosis of more than one year
- Exclusion criteria: Eating disorder, pregnant and/or lactating people, alcohol use disorder, uncontrolled hypothyroidism, taking appetite-altering treatments, psychiatric diagnoses, as well as patients unable to communicate
- Participants were given a semi-structured questionnaire to assess intuitive eating scored according to the Intuitive Eating Scale 2 (IES-2; 23 question survey on eating attitudes, with each question rated on five-point scale ranging from strongly disagree to strongly agree, where a higher score indicates a more intuitive eating style). Components addressed included unconditional permission to eat desired food when hungry, classifying the food as neutral, eating for physical and non-emotional reasons, reliance on hunger cues to determine when and how much to eat.
- Logistic regression was used to assess the association between intuitive eating score and glycemic control (defined as HbA1c <7%).

INTERVENTION (# IN THE GROUP): Not available
COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Not available

RESULTS:

- Patients with the highest intuitive eating scores on the IES-2 scale had an 89% lower chance of presenting to clinic with inadequate glycemic control compared with those with the lowest intuitive eating scores (OR 0.11; 95% CI, 0.024–0.54).
- This relationship persisted after adjusting for BMI categories.

LIMITATIONS:

- Cross-sectional study limits assessment of causality.
- Small sample size
- Limited generalizability given specific patient population in university hospital endocrinology clinic in Brazil.
- Wide exclusion criteria may limit generalizability.
- Predominantly female study population

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