GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 23

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of June 5 - 9, 2023

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- The Effect of Opioid Use on Obstructive Sleep Apnea

An RSV Vaccine for the Geriatric Population

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy and Safety of an Ad26.RSV.preF-RSV preF Protein Vaccine in Older Adults

Falsey AR, Williams K, Gymnopoulou E, et al. Efficacy and Safety of an Ad26.RSV.preF-RSV preF Protein Vaccine in Older Adults. *N Engl J Med*. 2023;388(7):609-620. doi:10.1056/NEJMoa2207566

KEY TAKEAWAY: The Ad26.RSV.preF–RSV preF protein vaccine is effective against RSV-mediated lower respiratory tract infections in older adults.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease in adults 65 and older. However, no existing RSV vaccine exists for this population.

PATIENTS: Adults 65 years old or older

INTERVENTION: RSV vaccine

CONTROL: Placebo

PRIMARY OUTCOME: Vaccine efficacy based on the first occurrence of symptomatic, PCR-confirmed RSV-mediated lower respiratory tract infection (LRTI)
Secondary Outcome: Symptom scores, time to return to usual health, antibody titers, and any adverse event

METHODS (BRIEF DESCRIPTION):

- Eligible participants were over the age of 65 in good overall health. Participants with chronic medical conditions including diabetes, and mild to moderate cardiac, pulmonary, or renal disease were also included.
- Participants were excluded if they developed an RSV-mediated acute respiratory infection or stopped participation within 14 days of injection.
- Participants were randomized in a 1:1 ratio and stratified according to their risk level and age group.
- Participants were monitored twice weekly for new or worsening acute respiratory infection symptoms. Symptomatic participants completed a daily electronic diary using the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) and Return to Usual Health question from day 1 until symptom resolution or return to baseline for at least 2 days.
- On day 1 or 2 of symptoms, participants self-swabbed for RSV. On days 3, 4, or 5, nasal and sputum samples were collected. RT-PCR confirmation of RSV was performed with the FDA-approved test Cepheid.
- One of three case definitions was used to define the primary outcome:
  1) three or more LRTI symptoms (severe illness)
  2) two or more LRTI symptoms (moderate illness)
  3) two or more LRTI symptoms or one or more LRTI symptoms plus at least 1 systemic symptom (mild illness)
- LRTI symptoms included cough, shortness of breath or decreased oxygen saturation, sputum production, wheezing, and tachypnea (>20 breaths per minute). Systemic symptoms included fatigue, fever (temp >37.8C), and subjective fever.
- RSV A2, RSV B, preF IgG, and RSV-F-specific antibody levels were obtained on days 1, 15, 85, and 169 for 195 participants (97 in the vaccine group and 98 in the placebo group).
- Any serious adverse event or adverse events leading to participant discontinuation were collected for 6 months after the injection or until the end of RSV season, whichever was later.
- Serious adverse events included cardiac disorders, pneumonia, neurovascular disorders, metabolic disorders, musculoskeletal disorders, and gastrointestinal disorders.

INTERVENTION (# IN THE GROUP): 2,791

COMPARISON (# IN THE GROUP): 2,801

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- The vaccine was 80% efficacious for severe illness when compared to the placebo (94.2% CI, 52–93).
- The vaccine was 75% efficacious for moderate illness when compared to the placebo (94.25% CI, 50–89).
- The vaccine was 69.85% efficacious for mild illness when compared to the placebo (94.2% CI, 44–85).

Secondary Outcome –

- RiiQ symptom scores were lower for the vaccinated group when compared to the placebo (39 vs 128).

- Time to return to usual health was lower for the vaccinated group compared to the control group (19 days vs 30 days; HR 2.81; 95% CI 1.01-7.86)
- Immunogenicity:
  - RSV A2 antibodies increased by a factor of 12.1 on day 15 and remained 5.5 times above baseline on day 169.
  - RSV B antibodies increased by a factor of 10.4 on day 15 and remained 4.4 times above baseline by day 169.
  - RSV preF IgG antibodies increased by a factor of 14.3 on day 15 and remained 5 times above baseline by day 169.
  - There were no changes in immunogenicity measured in the placebo group.
- Adverse events:
  - Local adverse events were higher in the vaccine group. The most common adverse event was injection site pain or tenderness.
  - Systemic adverse events were higher in the vaccine group compared to the control group. The most common systemic adverse events were fatigue, headache, and myalgia.

LIMITATIONS:

- The surveillance period was shortened due to the COVID-19 pandemic.
- There was an underrepresentation of minority populations (e.g. Black, Hispanic, Asian) in the participant demographic
- The study was sponsored by Janssen Vaccines and Prevention, who also manufacture the vaccine.

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The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at Large, or the Department of Defense.

Targeting Triglycerides: Does Pemafibrate Prevail?

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

Das Pradhan A, Glynn RJ, Fruchart JC, et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N Engl J Med*. 2022;387(21):1923-1934. doi:10.1056/NEJMoa2210645

KEY TAKEAWAY: Decreasing Type 2 Diabetes Mellitus (T2DM) patients' total triglyceride levels with pemafibrate does not significantly decrease adverse cardiovascular events.

STUDY DESIGN: Multinational, double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Increased triglyceride levels are associated with an increased incidence of adverse cardiovascular events; however, it has not been studied whether decreasing them reduces this risk. Previously, studies have shown that high dose n-3 fatty acid, niacin, and fenofibrate do not decrease cardiovascular adverse events despite a 20-30% decrease in triglyceride levels. This study had the same aim but with pemafibrate, a potent and selective peroxisome proliferator–activated receptor α (PPARα) modulator.

PATIENTS: Adults with T2DM, hypertriglyceridemia, and low HDL

INTERVENTION: Pemafibrate

CONTROL: Placebo

PRIMARY OUTCOME: Cardiovascular events

Secondary Outcome: Total triglycerides, adverse renal events, venous thromboembolism (VTE), LDL

METHODS (BRIEF DESCRIPTION):

- Both adult men and women were recruited with the following inclusion criteria: Type 2 DM, hypertriglyceridemia 200-499 mg/deciliter, and HDL of 40mg or below
  - Primary-prevention cohort: Men >50, women >55 without atherosclerotic cardiovascular disease
  - Secondary-prevention cohort: men and women >18 with established cardiovascular disease
- Exclusion criteria: uncontrolled T2DM, T1DM, severe renal disease, severe liver disease, severe congestive heart failure
- All members participated in a 21 day placebo run to assess adherence to oral medication
- Patients were randomly assigned via computer algorithm to treatment vs. placebo group in 1:1 ratio
  - Stratification parameters set for sex, cardiovascular history, and statin use
  - If on mod/high-intensity statin: LDL needed to be <70
  - If unable to be on a statin: LDL needed to be <100
- Primary endpoints: decrease in the incidence of initial cardiovascular event defined as:
  - non-fatal myocardial infarction
  - ischemic stroke
  - unstable angina needing coronary revascularization
  - death from CV causes
- Alternating in-person and telehealth follow-up was conducted at 2, 4, 6, 8, and 12 months and then every 4 months after to inquire about end-point events.

INTERVENTION (# IN THE GROUP): 5,240

COMPARISON (# IN THE GROUP): 5,257

FOLLOW-UP PERIOD: Median 3.4 years

RESULTS:

Primary Outcome –

- Pemafibrate did not significantly reduce adverse cardiovascular events compared to placebo (Hazard Ratio [HR] 1.0; 95% CI, 0.91–1.2).

Secondary Outcome –

- Pemafibrate did decrease overall triglyceride levels by 26.2% compared to placebo (95% CI, 24–28).
- Pemafibrate significantly increased the number of adverse renal events compared to placebo (HR 1.1; 95% CI, 1.04–1.2).
- Pemafibrate significantly increased VTE compared to placebo (HR 2.1; 95% CI, 1.4–3.2).
- Patients taking pemafibrate had a 12.3% increase in LDL levels compared to placebo (95% CI, 11–14).

LIMITATIONS:

- The study design excluded patients with uncontrolled T2DM which may be a patient population for which cardiovascular adverse events

would be decreased with more stringent triglyceride control. Median A1c was 7.3.

- In the general population, very few patients have a diagnosis of T2DM without chronic kidney disease, congestive heart failure, or liver disease, making this study population a very specific representation for the average practitioner's patient panel.
- The study was largely unrepresentative of the Black population as the treatment group and placebo group were 85-86% White and only 2.5-2.6% Black which does not correlate to the general population with T2DM where non-Hispanic Black patients have a higher incidence of T2DM compared to non-Hispanic White patients.

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Can a Mediterranean Diet Really Affect Biomarkers of Alzheimer's Disease?

Mediterranean and Western Diet Effects on Alzheimer's Disease Biomarkers, Cerebral Perfusion, and Cognition in Mid-Life: A Randomized Trial

Hoscheidt S, Sanderlin AH, Baker LD, et al. Mediterranean and Western diet effects on Alzheimer's disease biomarkers, cerebral perfusion, and cognition in mid-life: A randomized trial. *Alzheimers Dement*. 2022;18(3):457-468. doi:10.1002/alz.12421

KEY TAKEAWAY: Adherence to a Mediterranean-like diet in adults with normal cognition had beneficial effects on CSF biomarkers of Alzheimer's disease (AD) and cerebral perfusion compared to a Western diet. Adults with mild cognitive impairment experienced opposite trends in CSF biomarkers, possibly due to increased reliance on lipid metabolism in early-stage AD.

STUDY DESIGN: Double-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded as outcomes are disease-oriented and not patient-oriented)

BRIEF BACKGROUND INFORMATION: Alzheimer's disease is the leading cause of dementia and sixth most common cause of death in the United States. Epidemiologic studies have shown associations between diets high in saturated fats and simple carbohydrates and AD. This study was designed to investigate whether a Mediterranean diet can affect AD risk as measured by CSF biomarkers, cerebral perfusion, and cognition.

PATIENTS: Adults with normal cognition (NC) or mild cognitive impairment (MCI)

INTERVENTION: Mediterranean Diet

CONTROL: Western Diet

PRIMARY OUTCOME: CSF $(A\beta)_{42/40}$ ratio, total tau (t-tau), cerebral perfusion, cognition

Secondary Outcome: Serum total cholesterol, LDL, HDL, insulin, glucose, and A1c

METHODS (BRIEF DESCRIPTION):

- 87 adults between ages 45 and 65 recruited from Winston-Salem, NA or Seattle, WA were included.
  - 56 had normal cognition.
  - 31 had mild cognitive impairment.
- Baseline serologic testing was performed.
- They were randomly assigned to dietary groups and provided with an isocaloric Mediterranean-like diet or Western diet prepared by the dietary kitchen to mask the treatment condition.
- The Mediterranean-like diet was low in saturated fat, glycemic index, and sodium and high in healthy fats, whole grains, fruits, and vegetables.
  - The Western diet was high in saturated fat, glycemic index, and sodium.
- Food diaries were provided to track diet compliance.
- Serologic testing, lumbar puncture, pcASL-MRI for cerebral perfusion, and cognitive testing were performed after four weeks of dietary intervention.

INTERVENTION (# IN THE GROUP): 41

COMPARISON (# IN THE GROUP): 43

FOLLOW-UP PERIOD: After diet ended, no prolonged follow up

RESULTS:

Primary Outcome –

- In adults with normal cognition:
  - Total CSF $(A\beta)_{42/40}$ was decreased after eating the Mediterranean diet and increased after eating the Western diet ($F_{[1,41]}$= 5.3, *P*=.026).
  - The CSF $(A\beta)_{42/40}$ ratio was increased (associated with less AD risk) by the Mediterranean diet and decreased (more AD risk) by the Western diet ($F_{[1,41]}$= 6.6, *P*=.014).
  - Whole brain cerebral perfusion increased after eating the Mediterranean diet and decreased after eating the Western diet ($F_{[1,31]}$=0.12, *P*= .003).
  - No significant association was found between cognition and diet ($F_{[1,45]}$=3.3, *P*=.077).
- Adults with mild cognitive impairment showed opposite patterns in CSF biomarkers.
  - CSF total tau was increased by the Mediterranean diet and decreased by the Western diet ($F_{[1,20]}$= 4.6, *P*=.044).
  - The $(A\beta)_{42/40}$ total tau ratio was increased (lower AD risk) by the Western diet compared to the Mediterranean diet ($F_{[1,20]}$=5.1, *P*=.036).
  - $(A\beta)_{42/40}$ ratio trended toward increasing with the Western diet and decreasing with the Mediterranean diet ($F_{[1,23]}$=3.8, *P*=.064).

Secondary Outcome –

- In all participants, compared to the Mediterranean diet, the Western diet was associated with:
  - Higher serum total cholesterol ($F_{[1,69]}$=22, *P*=.0001).
  - Higher LDL ($F_{[1,68]}$= 27, *P*=.0001).
  - Higher HDL ($F_{[1,72]}$= 13, *P*=.0006).

LIMITATIONS:

- Patients with hyperlipidemia, hypertension, diabetes, or significant neurologic disease were excluded.
- The sample size was relatively small.
- The study was relatively short (4 weeks), limiting the possible long-term, counter-regulatory effects of the Mediterranean diet or Western diet on participants, particularly those with MCI.

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The Effect of Opioid Use on Obstructive Sleep Apnea

The Relationship Between Opioid Use and Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

Ahmad A, Ahmad R, Meteb M, et al. The relationship between opioid use and obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2021;58:101441. doi:10.1016/j.smrv.2021.101441

KEY TAKEAWAY: Opioid use likely does not affect obstructive sleep apnea (OSA).

STUDY DESIGN: Systematic review and meta-analysis of 15 studies (6 clinical trials and 9 observational; N=1255)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to low-quality studies and heterogeneity)

BRIEF BACKGROUND INFORMATION: Opioids cause a dose-dependent respiratory depression that is more pronounced during sleep. Therefore, it has been proposed that opioids are able to induce or aggravate sleep-disordered breathing. While the relationship between opioids and central apnea has been adequately covered in the literature, this review focuses on the much less explored association between opioids and OSA.

PATIENTS: Adults with OSA diagnosis

INTERVENTION: Opioid use

CONTROL: No opioid use

PRIMARY OUTCOME: OSA severity

Secondary Outcome: Polysomnographic measures of OSA severity, sleep quality, daytime sleepiness

METHODS (BRIEF DESCRIPTION):

- Peer-reviewed longitudinal studies in English published from 1946 to 2018 were considered for the literature search.
- Selected studies included randomized controlled trials and observational studies with both male and female participants over 18 years old with OSA.
- Studies including opioid antagonists or anesthetic drugs were excluded.
- Morphine equivalent dosages for the included studies ranged between 4 mg and 200 mg. Participants used morphine and methadone in 60% of the studies, fentanyl, and hydromorphone in 40%, oxycodone in 33%, and hydrocodone in 13%.
- Outcome measurements:
  - OSA Severity was measured using the change in mean Apnea-Hypopnea Index (AHI) with opioid use.
  - Polysomnographic measures of OSA severity (other than the AHI) included oxygen desaturation index, respiratory disturbance index, time spent with oxygen saturation less than 90%, minimum oxygen saturation during sleep, apnea index, hypopnea index, and respiratory effort-related arousal index.
  - Measures of sleep quality and architecture included total sleep time, sleep efficiency, wake after sleep onset, percentage and duration of sleep stages, arousal index, and the number of awakenings.
  - Measures of daytime sleepiness included Epworth sleepiness score, multiple sleep latency, and maintenance of wakefulness test.

INTERVENTION (# IN THE GROUP): 1,038

COMPARISON (# IN THE GROUP): 217

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Opioid use does not have a worsening effect on the severity of OSA (estimated mean difference 1.5; 95% CI, –2.6 to 5.6; I^2=65%).

Secondary Outcome –

- When using polysomnographic measurements, the effects of opioids on OSA were unclear.
- Patients had reduced daytime sleepiness as measured by a reduction in ESS, from 12.5 ± 1.5 down to 7.5 ± 2.2.

LIMITATIONS:

- The paucity of good-quality studies constrained the findings of this review.
- Most studies were limited to small sample sizes, selection bias, and incomplete data.
- High heterogeneity resulted in underutilizing the already limited number of studies included in the review for analysis.
- Meta-analyses to assess the PAP effect along with polysomnographic measures of severity of OSA other than the AHI were not performed due to insufficient and limited data.

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