GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of June 20 - 24, 2022

SPOTLIGHT: Mirtazapine for Agitation in Patients with Alzheimer's

Mirtazapine for Agitation in Patients with Alzheimer's

Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial

Banerjee S, High J, Stirling S, et al. Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2021; 398(10310):1487–1497. doi:10.1016/S0140-6736(21)01210-1

KEY TAKEAWAY: Mirtazapine does not improve agitation in patients with Alzheimer's dementia.

STUDY DESIGN: Multi-site, parallel group, double-blind, placebo controlled randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Agitation is a difficult and common comorbidity in patients diagnosed with Alzheimer's disease. When non-pharmacologic interventions fail, there is little evidence to support the use of pharmacologic therapy but many known harms. Mirtazapine is a common medication used for agitation, but no studies exist to assess the efficacy.

PATIENTS: Adults with Alzheimer's disease and coexisting agitation

INTERVENTION: Mirtazapine up to 45 mg daily

CONTROL: Placebo

OUTCOME: Reduction in agitation at 12 weeks

Secondary Outcome: Cognition, quality of life, neuropsychiatric symptoms

METHODS (BRIEF DESCRIPTION):

- Alzheimer's criteria were based on the National Institute of Neurological and Communicative Diseases and Stroke diagnostic criteria. Alzheimer's diagnosis and agitation was not due to another cause.
- Participants were assessed in their homes or other agreed settings. Some participants were assessed via phone during the COVID-19 lock down.
- Agitation was defined using a Cohen-Mansfield Agitation Inventory (CMAI) score of 45 or more. The CMAI score is a 29-item questionnaire that is rated by a primary caregiver.
- Agitation scores were measured at baseline, six weeks, and 12 weeks.
- Participants were assigned to receive placebo or up to 45 mg daily mirtazapine in addition to their normal treatment regimen.
- The mirtazapine group started at 15 mg daily and was gradually increased to 45 mg daily over four weeks. At weeks two and four, researchers contacted caregivers to assess adverse effects and adherence. If participants had significant side effects, they either remained on the current dose or stopped the medication.

INTERVENTION (# IN THE GROUP): 81

COMPARISON (# IN THE GROUP): 90

FOLLOW UP PERIOD: Six and 12 weeks

RESULTS:

Primary Outcome –

- Although there was a reduction in agitation scores for both groups at six and 12 weeks, there was no significant difference between mirtazapine and placebo (61 vs 61; adjusted mean difference -1.7; 95% CI, -7.2 to 3.7).

Secondary Outcomes –

- No statistically significant difference in cognition, quality of life, or neuropsychiatric symptoms such as depression and anxiety.
- Potential increased mortality in intervention group, although not statistically significant. No other significant difference in adverse events.

LIMITATIONS:

- The study was not powered to evaluate a mortality difference, so the weak association was likely related to chance.
- The trial took place during the COVID-19 pandemic, which led to adjustments in the trial protocol and introduced additional environmental factors.
- Most study participants were in care homes, not dwelling within the community.

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Caffeine Use in Pregnancy

Assessment of Caffeine Consumption and Maternal Cardiometabolic Pregnancy Complications

Hinkle SN, Gleason JL, Yisahak SF, et al. Assessment of Caffeine Consumption and Maternal Cardiometabolic Pregnancy Complications. *JAMA Netw Open*. 2021; 4(11):e2133401. Published 2021 Nov 1. doi:10.1001/jamanetworkopen.2021.33401

KEY TAKEAWAY: Caffeine intake <200 mg/day (within the recommended range) in the second trimester is associated with a decreased risk of Gestational Diabetes Mellitus (GDM) but is not associated with development of gestational hypertension or preeclampsia.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current recommendations suggest limiting caffeine intake in pregnancy to less than 200 mg/day based on risk of adverse fetal outcomes at higher intake levels including fetal growth restriction, miscarriage, and pre-term delivery. Little information is available regarding maternal outcomes of caffeine use. This study aims to determine if maternal cardiometabolic complications are associated with caffeine use in pregnancy.

PATIENTS: Pregnant women

INTERVENTION: Caffeine consumption (1-100 mg/day; 101-200 mg/day; >200 mg/day)

CONTROL: No consumption of caffeine (0 mg/day)

OUTCOME: Cardiometabolic complications (gestational diabetes, gestational hypertension, preeclampsia)

METHODS (BRIEF DESCRIPTION):

- 2,583 pregnant women between 8–13 weeks gestation enrolled at 12 U.S. clinical centers.
- Secondary analysis of NICHD Fetal Growth Studies-Singleton Cohort (n=2,802) aiming to establish race and ethnicity-specific standards for fetal growth.
- Eligibility:
  - BMI 19–29: non-smoker, no drugs, no alcohol, natural conception, no prior pregnancy complications, otherwise healthy
  - BMI 30-45: limited to women without major chronic diseases
- Questionnaires and exams at enrollment, 16–22 wks, 24–29 wks, 30–33 wks, 34–37 wks, and delivery. Labs collected at enrollment and visits one, two, and four.
- Determining exposure:
  - Self-reported intake of cups of caffeinated coffee, tea, and cans/bottles of caffeinated soda/energy drinks multiplied by estimated caffeine content in each type of beverage.
  - Plasma caffeine and plasma paraxanthine collected at 10–13 wks.
- Determining Primary Outcomes:
  - Blood pressure measurements reviewed in medical record to determine clinical diagnoses of gestational hypertension and preeclampsia
  - Gestational Diabetes (positive OGTT by Carpenter-Coustan criteria and/or treatment with diabetes medications)
  - Impaired Glucose Tolerance (2-hour OGTT glucose 140-199 mg/dL but not meeting GDM criteria)

INTERVENTION (# IN THE GROUP):

Caffeine intake at 10–13 weeks

- 1-100 mg/day: 1,317
- 101-200 mg/day: 173
- >200 mg/day: 20

Caffeine intake at 16–22 weeks

- 1-100 mg/day: 1,734
- 101-200 mg/day: 186
- >200 mg/day: 20

COMPARISON (# IN THE GROUP): 1,073 (10–13 weeks), 599 (16–22 weeks)

FOLLOW UP PERIOD: Pregnancy at enrollment through delivery, enrollment from 2009-2013, statistical analysis completed in 2021

RESULTS:

- Compared to no caffeine, caffeine intake at 10–13wks was not associated with GDM, preeclampsia, or gestational hypertension.
- Caffeine was not associated with increased blood pressure, gestational hypertension, or preeclampsia throughout pregnancy.
- Compared to no caffeine, caffeine intake 1-100 mg/day at 16–22wks was associated with:
  - Lower GDM risk: RR 0.53 (95% CI, 0.35–0.80)
  - Lower glucose concentrations in glucose challenge: -2.7 mg/dL (95% CI, -5.4 mg/dL to 0 mg/dL)

LIMITATIONS:

- Observational data, residual confounders may exist despite adjustment for major known confounders.

- Data relies on self-reported exposure from beverages only, does not include other sources of caffeine.
- Category of caffeine intake >200 mg/dL had very few women, difficult to assess risk in higher levels of caffeine intake.
- Due to sample size, analyses by beverage type could not be performed.
- Unable to assess timing of caffeine intake and risk of gestational hypertension/preeclampsia because timing of diagnosis was unknown (collected via chart review).
- Did not study caffeine intake in third trimester.
- Did not report on adverse fetal outcomes which are known risks of caffeine intake.

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Subcutaneous Semaglutide May Treat Histologic Findings in NASH

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med.* 2021; 384(12):1113-1124. doi:10.1056/NEJMoa2028395

KEY TAKEAWAY: Subcutaneous semaglutide can result in histologic resolution of nonalcoholic steatohepatitis (NASH) without the worsening of fibrosis.

STUDY DESIGN: Double-blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of patient-oriented outcomes)

BRIEF BACKGROUND INFORMATION: Despite the high morbidity/mortality of NASH, no drugs are currently approved for treatment. Insulin resistance is thought to play a role in pathogenesis. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has previously been shown to histologically improve NASH as well as liver enzymes.

PATIENTS: Adults with biopsy-confirmed NASH

INTERVENTION: Subcutaneous semaglutide at 0.1 mg, 0.2 mg, or 0.4 mg

CONTROL: Placebo

OUTCOME: Histologic improvement in NASH without worsening of fibrosis

METHODS (BRIEF DESCRIPTION):

- Participants were randomized to receive either 0.1 mg, 0.2 mg, or 0.4 mg subcutaneous semaglutide daily, or placebo.
- Participants had a baseline liver biopsy prior to taking semaglutide or placebo to establish level of NASH and fibrosis.
- Participants had repeat liver biopsy at 72 weeks to reassess NASH parameters and fibrosis.
- All participants received dietary/lifestyle counseling throughout the trial period.

INTERVENTION (# IN THE GROUP):

- 0.1 mg group: 80
- 0.2 mg group: 78
- 0.4 mg group: 82

COMPARISON (# IN THE GROUP): 80

FOLLOW UP PERIOD: 72 Weeks

RESULTS:

- Semaglutide 0.4 mg daily increased histologic resolution of NASH without worsening liver fibrosis when compared to placebo (OR 6.9; 95% CI, 2.6–18).
- Semaglutide 0.4 mg daily did not significantly improve fibrosis stage without histologic worsening of NASH compared to placebo (OR 1.4; 95% CI, 0.62–3.3).
- Comparisons between placebo, 0.1 mg, and 0.2 mg dose groups not performed due to the lack of significance in fibrosis improvement with 0.4 mg dose group; based on pre-determined analysis hierarchy to address concerns of multiplicity.

LIMITATIONS:

- Unclear if primary and secondary outcomes affect patient morbidity or mortality.
- Study funded by Novo Nordisk, makers of semaglutide.
- Despite being a multi-national study, most participants were white (78%) and female (61%).
- Pathologists initially only agreed on all parameters 24% of the time.
- Lack of improvement in fibrosis without worsening of NASH in the 0.4 mg group was unexpected based on previous studies, and limited further analysis based on pre-determined hierarchy.

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Is the mRNA-1273 SARS-CoV-2 Vaccine Safe & Effective in Adolescents?

Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents

Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. *N Engl J Med*. 2021; 385(24):2241–2251. doi:10.1056/NEJMoa2109522

KEY TAKEAWAY: The mRNA-1273 vaccine was determined to have an acceptable safety profile in adolescents. The immune response was similar to that in young adults and the vaccine was efficacious in preventing COVID-19.

STUDY DESIGN: Ongoing phase 2-3, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Most COVID-19 vaccination information including safety, immunogenicity and efficacy were studied in young adults, hence making the information in regard to the adolescent age range essentially unknown.

PATIENTS: Healthy adolescents ages 12–17 years old

INTERVENTION: mRNA -1273 vaccine

CONTROL: Placebo (saline)

OUTCOME: Safety, non-inferiority of immunogenicity

Secondary Outcome: Efficacy

METHODS (BRIEF DESCRIPTION):

- Participants were randomly assigned in a 2:1 ratio to receive either 2 doses of mRNA-1273 or saline (placebo). Doses were separated by 28 days.
- Investigators, participants, and all investigative staff were double blinded. Pharmacist and vaccine administrators who were only involved in administration were the only ones aware of these assignments.
- Vaccine safety was examined based on adverse events (including injection site lymphadenopathy and headaches) that were logged by participants electronically (day one through day 28 after each injection).
- Immunogenicity was assessed via serum antibody responses, mean titer ratio of neutralizing antibody titer and serological response 28 days after receiving the second dose.
- Adolescent immunogenicity was compared to young adult immunogenicity based on neutralizing antibody titers.
- Vaccine efficacy was also measured with the incidences of Covid-19 and asymptomatic SARS-CoV-2 infection within 14 days after second dose.

INTERVENTION (# IN THE GROUP): 2,489

COMPARISON (# IN THE GROUP): 1,243

FOLLOW UP PERIOD: 53 days observation period after 2nd dose of vaccine

RESULTS:

- Vaccine Safety: Incidence of Unsolicited AEs up to 28 Days After Any Injection – including symptomatic complaints.
  - Local reaction (pain)
    - After 1st injection – (93%)
    - After 2nd injection – (92%)
    - Placebo (saline) – (35% & 30%)
  - Systemic adverse reactions (fatigue, headaches, myalgia, chills)
    - After 1st injection – (69%)
    - After 2nd injection – (86%)
    - Placebo (saline): Headache (39% and 30%) and fatigue (37% and 29%).
  - Immunogenicity amongst adolescents were non-inferior compared to young adults (age 18–25 years old) – this was based on
    - Geometric mean titer (1.0 (95% CI, 0.94–1.2)
    - Serological response (absolute difference 0.2% (95% CI, -1.8 to 2.4)

No reported case of myocarditis or pericarditis in participants that received the mRNA-1273 vaccine.

LIMITATIONS:

- Efficacy analysis was limited as there are milder COVID-19 disease symptoms and lower disease incidences in adolescents compared to adult.
- Difficulty comparing results from mRNA-1273 (Moderna) vs BNT162b2 (Pfizer).
- Trial population was less diverse (84% white) in the phase 3 trial, hence less representative of the US population.
- P-values and 95% CI not provided in vaccine safety data.

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A Take on Angiotensin Receptor-Neprilysin Inhibitors in the Setting of Acute Myocardial Infarctions

Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction

Pfeffer MA, Claggett B, Lewis EF, et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction [published correction appears in N Engl J Med. 2021 Dec 30; 385(27):2592]. *N Engl J Med.* 2021; 385(20):1845-1855. doi:10.1056/NEJMoa2104508

KEY TAKEAWAY: Sacubitril-valsartan does not lower the incidence of cardiovascular death compared to ramipril in patients who had acute myocardial infarction.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: It is known that angiotensin converting-enzyme inhibitors (ACE-I) when compared to placebo, have relative benefits in the setting of an acute myocardial infarction and reduces risks of cardiovascular events afterwards. Angiotensin-receptor-neprilysin inhibitors (ARN-I) act in similar ways to ACE-I in terms of inhibiting the renin-angiotensin pathway and are known to reduce risk of episodes of deterioration in patients with heart failure. This study aims to study the benefit of ARN-I vs ACE-I in patients with acute myocardial infarctions and heart failure with reduced ejection fraction.

PATIENTS: Patients with acute myocardial infarction and/or heart failure with reduced ejection fraction

INTERVENTION: ARN-I

CONTROL: ACE-I

OUTCOME: Death from cardiovascular causes

Secondary Outcomes: Hospitalization from myocardial infarction (MI), stroke

METHODS (BRIEF DESCRIPTION):

- Patients had an average age of 64 years old, 24% female, history of HFrEF (LVEF <= 40%), had an acute MI 0.5–7 days before presentation, and had at least one "risk-augmenting factor" (diabetes, previous MI, ≥70 years old, GFR < 60, atrial fibrillation, STEMI without reperfusion within 24 hours).
- The treatment group received either sacubitril-valsartan or ramipril.
- Evaluations were scheduled for week one, week two, week four, month two, month four, and then every four months after that for a total of 22 months.
- Three doses of each medication were available to the investigator, and the highest dose of each drug was the target dose.
- The primary outcome was measured by death from cardiovascular causes or incident heart failure (first hospitalizations from heart failure or outpatient symptomatic heart failure).
- Secondary outcomes included hospitalizations from MI and stroke.

INTERVENTION (# IN THE GROUP): 2,830

COMPARISON (# IN THE GROUP): 2,831

FOLLOW UP PERIOD: 22 months

RESULTS:

Primary Outcome –

- Sacubitril-valsartan did not lower the rate of cardiovascular death, heart failure hospitalization, or outpatient heart failure requiring treatment compared to ramipril (HR 0.90; 95% CI, 0.78–1.0).

Secondary Outcome –

- Death from cardiovascular causes alone and death from any cause did not differ significantly between groups.

LIMITATIONS:

- The study population did not reflect general population.
- The study did not adjust or differentiate between ischemic vs non-ischemic causes of heart failure.

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