GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 4 - 8, 2022

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CKD and CHF: What's Known About Finerenone?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med.* 2021;385(24):2252-2263. doi:10.1056/NEJMoa2110956

KEY TAKEAWAY: Finerenone improved cardiovascular outcomes compared to placebo for patients with diabetes mellitus type 2 with stage 2 to stage 4 chronic kidney disease (CKD) with moderately elevated albuminuria and patients with stage 1 to stage 2 CKD with severely elevated albuminuria.

STUDY DESIGN: Phase three, multicenter, randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Finerenone, a mineralocorticoid receptor antagonist, is beneficial for patients with CKD stage 3 and 4 for its cardiorenal properties but the cardiorenal protective efficacies and benefits are unknown in patients with CKD stage 2 to 4 with moderate albuminuria or CKD stage 1 to 2 with severe albuminuria secondary to diabetes.

PATIENTS: Adults with CKD and diabetes

INTERVENTION: Finerenone

CONTROL: Placebo

OUTCOME: Composite of death from cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, hospitalization due to heart failure

METHODS (BRIEF DESCRIPTION):

- 7,437 patients across 48 countries were randomized from September 2015 to October 2018.
  - Patients were 18 years old and older with an average age of 64.
  - Patients had CKD secondary to diabetes mellitus type 2 and currently treated with a renin-angiotensin system inhibitor on maximum dose, or RAS therapy titrated to maximum tolerated prior to randomization.
  - About 70% of patients were male and 70% of study participants were White with an average HbA1c of 7.7%.
- One group of patients consisted of persistent, moderately elevated albuminuria, defined as urine albumin-to-creatinine ratio (ACR) 30-300.
- Second group of patients consisted of persistent, severely elevated albuminuria, defined as urine ACR 300-5,000.
- Both groups had potassium levels less than 4.8 mmol/L.
- Patients were randomized to finereone or placebo.

INTERVENTION (# IN THE GROUP): 3,686

COMPARISON (# IN THE GROUP): 3,666

FOLLOW UP PERIOD: Median of 3.4 years

RESULTS:

- Patients in the finerenone group had lower risk of the composite outcome (12% finerenone group vs 14% in placebo group; Hazard ratio [HR] 0.87; 95% CI, 0.76–0.98; NNT=56).
- Incidence of hospitalization for heart failure was lower in finerenone group than placebo group (3.2% finerenone vs 4.4% placebo; HR 0.71; 95% CI, 0.56–0.90; NNT=83).

LIMITATIONS:

- Did not address any potential lifestyle modifications in terms of low salt diet or other diet forms.
- Aside from patients maxed out on ACE-I or ARB, there were no descriptions of other medications in the setting of CHF or CKD medications outside of the ACE-I or ARB.
- Patient population predominantly White and may not be generalizable to other populations.
- Study was shortened due to COVID-19 pandemic.

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Don't Sleep on this New Class of Anti-Insomnia Agents: Dual Orexin Receptor Antagonists

Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial

Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial [published correction appears in *JAMA Netw Open*. 2020 Apr 1;3(4):e206497] [published correction appears in *JAMA Netw Open*. 2021 Aug 2;4(8):e2127643]. *JAMA Netw Open*. 2019; 2(12):e1918254. Published 2019 Dec 2. doi:10.1001/jamanetworkopen.2019.18254

KEY TAKEAWAY: Dual orexin receptor antagonists (DORA) are a new class of anti-insomnia medications. Lemborexant, a DORA, at both 5 mg and 10 mg demonstrated statistically significant improvement in time to persistent sleep and sleep efficiency compared to placebo. It was shown to be superior to Zolpidem in its ability to increase sleep efficiency.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Insomnia is a debilitating condition that affects a significant percentage of the population, including the elderly. Current management including first line treatment with cognitive behavioral therapy (CBT) may not work well for or be accessible to many patients. Traditional pharmacological therapy that targets GABA and histamine receptors may only address either sleep initiation or sleep maintenance. These agents also come with side effects such as dependence, withdrawal, and delirium, with increased risk to members of the elderly population. Orexin receptor antagonists are a relatively new class of medications whose effect reduces the drive to stay awake. To determine efficacy of insomnia medications like DORAs, metrics including latency to persistent sleep and sleep efficiency (total amount of time asleep while in bed) can be used.

PATIENTS: Adults who meet DSM-5 criteria for insomnia

INTERVENTION: Lemborexant 5 mg, Lemborexant 10 mg

CONTROL: Placebo, Zolpidem 6.25 mg

OUTCOME: Latency to persistent sleep compared to placebo

Secondary Outcome: Sleep efficiency compared to Zolpidem

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria (must meet each bullet point):
  - Women 55 years old and older and men 65 years old and older
  - Meets DSM-5 criteria for insomnia
  - Have a subjective wake after sleep onset of 60 minutes or more for at least three nights per week during the last four weeks
  - Time spent in bed of 7-9 hours and Insomnia Severity Index of 13 or greater confirmed by PSG (polysomnography)
- Conducted over 67 locations in North America and Europe.
- All participants were initially treated with two weeks of placebo to exclude placebo responders as well as those who did not adhere to sleep diary instructions.
- Participants were randomized in a double-blinded double-dummy manner and placed into groups to receive either Lemborexant 5 mg or 10 mg, Zolpidem 6.25 mg, or placebo.
- Patients were treated for 30 days, taking one dose nightly.
- They completed an electronic sleep diary within one hour of waking up every morning.
- PSGs and sleep diaries were analyzed to measure primary and secondary outcomes.
- Latency to persistent sleep is non-normally distributed (asymmetrical distribution when graphed, as compared to normal distribution, which follows the more traditional symmetric bell-shaped distribution), so least square geometric means (LGSM) were used to compare value.

INTERVENTION (# IN THE GROUP):

- Lemborexant 5 mg: 266
- Lemborexant 10 mg: 269

COMPARISON (# IN THE GROUP):

- Placebo: 208
- Zolpidem 6.25 mg: 263

FOLLOW UP PERIOD: Evaluated by PSG on nights one, two, 29, and 30 of treatment. Followed by a follow up period of 14–18 days before the end of study visit.

RESULTS:

Primary Outcome –

- Compared to placebo, Lemborexant 5 mg and 10 mg both resulted in a significant decrease in latency to persistent sleep from baseline in the grouped data

from days one and two. In the grouped data at the end of the trial, days 29 and 30, the decrease was still significant and an even greater decrease from baseline was noted than at the initiation of treatment:
    - At days one and two, Lemborexant 5 mg led to a 17 min decrease from baseline (LGSM treatment ratio 0.85, 95% CI, 0.75–0.96).
    - At days one and two, Lemborexant 10 mg led to a 20 min decrease from baseline (LGSM treatment ratio 0.8, 95% CI, 0.70–0.90).
    - At days 29 and 30, Lemborexant 5 mg led to a 20 min decrease from baseline (LGSM treatment ratio 0.77, 95% CI, 0.67–0.89).
    - At days 29 and 30, Lemborexant 10 mg led to a 22 min decrease from baseline (LGSM treatment ratio 0.72, 95% CI, 0.52–0.83).

Secondary Outcome –

- Compared to Zolpidem, both doses of Lemborexant led to an increase in sleep efficiency as measured by percent of time in bed asleep.
    - At days one and two, Lemborexant 5 mg led to an increase in sleep efficiency (mean difference [MD] 2.1%; 95% CI, 0.8– 3.3).
    - At days one and two, Lemborexant 10 mg led to greater sleep efficiency (MD 4.6%; 95% CI, 3.4–4.9).
    - At days 29 and 30, Lemborexant 5 mg led to greater sleep efficiency (MD 3.9%; 95% CI, 2.5–5.3)
    - At days 29 and 30, Lemborexant 10 mg led to greater sleep efficiency (MD 4.9%; 95% CI, 3.5–6.3).

LIMITATIONS:

- Limited to patients 55 years old and older.
- Study lasted for only one month, limiting ability to evaluate long-term effects, especially for chronic conditions like insomnia.
- The utilization of hypnotic agents can affect the integrity of data collected that is based on participants' recall of event.
- Funded by a pharmaceutical company that produced Lemborexant.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense

Canagliflozin Improves Both Renal and Cardiovascular Outcomes

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744

KEY TAKEAWAY: In patients with type 2 diabetes and kidney disease, canagliflozin lowered the risk of cardiovascular events and the risk of kidney failure.

STUDY DESIGN: Double-blind, multicenter, RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus is the leading cause of kidney failure. There are few effective treatments available to lower the risk of kidney failure and cardiovascular events. Studies suggest that the sodium-glucose cotransporter 2 (SGLT2) drugs can reduce kidney failure and cardiovascular events in patients with type 2 diabetes

PATIENTS: Patients with type 2 diabetes mellitus, chronic kidney disease, and severely increased albuminuria

INTERVENTION: Canagliflozin

CONTROL: Placebo

OUTCOME: Composite of ESRD, doubling of creatinine levels, death from renal or cardiovascular causes

Secondary Outcome: Composite of cardiovascular death, myocardial infarction, or stroke; hospitalization for heart failure

METHODS (BRIEF DESCRIPTION):

- Patients with type 2 diabetes, chronic kidney disease (eGFR 30-90), and severely increased albuminuria (albumin/creatinine ratio > 300) were included if they had been on an ACE inhibitor or ARB for at least four weeks.
  - Patient demographics: Mean age 63 years old, 34% female, 67% White, 5% Black, 20% Asian
  - Comorbidities: Hypertension 97%, cardiovascular disease 50%, smokers 15%, heart failure 15%
- Patients received Canagliflozin 100 mg or placebo until trial completion, initiation of dialysis, pregnancy, kidney transplantation, or occurrence of diabetic ketoacidosis.
- After initial visits at weeks three, 13, and 26, follow up alternated between telephone calls and in-clinic visits every 13 weeks, with additional blood testing as needed.
- The trial was stopped early.

INTERVENTION (# IN THE GROUP): 2,202
COMPARISON (# IN THE GROUP): 2,199

FOLLOW UP PERIOD: 2.6 Years

RESULTS:

Primary Outcome –

- Canagliflozin significantly lowered the risk of the composite outcome compared to placebo (43 vs 61 per 1000 patient-years, respectively; hazard ratio [HR] 0.70; 95% CI, 0.59–0.82).

Secondary Outcomes –

- Canagliflozin significantly lowered the composite of cardiovascular death, myocardial infarction, or stroke (HR 0.80; 95% CI, 0.67–0.95).
- Canagliflozin significantly decreased hospitalizations for heart failure (HR 0.61; 95% CI, 0.47–0.80).

LIMITATIONS:

- The study did not measure off-treatment estimated eGFR levels among patients who completed the trial. It is not known if these eGFR levels remained favorable in the canagliflozin group as compared to the placebo group for the years after 2.7 years.
- This study did not examine patients with advanced kidney disease, kidney diseases due to conditions other than type 2 diabetes mellitus, and those who have non-albuminuric or microalbuminuric disease.
- Severely increased albuminuria is not commonly encountered in primary care.

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Another Reason Not to Catch COVID-19: Increased Risk of Preeclampsia

SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis

Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2022; 226(1):68-89.e3. doi:10.1016/j.ajog.2021.07.009

KEY TAKEAWAY: Infection with COVID-19 during pregnancy is associated with an increased risk for preeclampsia, preeclampsia with severe features, eclampsia, and HELLP syndrome.

STUDY DESIGN: Meta-analysis of 28 observational studies (N= 790,954)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Current evidence suggests that a pregnant patient's risk of preeclampsia increases with certain infections such as UTI's and periodontal disease, although a clear association with viral infections during pregnancy and preeclampsia has not been demonstrated. COVID-19 infections have been associated with adverse maternal and perinatal outcomes, but preeclampsia has not been investigated specifically.

PATIENTS: Pregnant women

INTERVENTION: COVID-19 infection during gestation

CONTROL: Absence of COVID-19 infection during gestation

OUTCOME: Preeclampsia

Secondary Outcomes: Preeclampsia with severe features, preeclampsia without severe features, eclampsia, and Hemolysis, Elevated Liver enzymes, and Low Platelet (HELLP) syndrome.

METHODS (BRIEF DESCRIPTION):

- The two authors performed literature reviews and meta-analyses of 28 observational studies of SARS-CoV-2 infection in pregnant patients in North America, Asia, Europe, South America, and one multi-country study.
- Studies included prospective cohorts, retrospective cohorts, and cross-sectional studies.
- SARS-CoV-2 infection was diagnosed via positive reverse transcriptase PCR, upper respiratory antigen, or serum anti-SARS-CoV-2 antibody test results.
- Prior to SARS-CoV-2 testing availability, participants were deemed "exposed" in the presence of clinical signs or symptoms and/or suggestive chest CT or X-Ray studies.
- SARS-CoV-2 infection was excluded with negative, reverse transcriptase PCR, upper respiratory antigen, or serum anti-SARS-CoV-2 antibody test results.
- Prior to SARS-CoV-2 testing availability, participants were deemed "not exposed" in the absence of clinical signs or symptoms and/or suggestive chest CT or X-Ray studies.
- The association between COVID-19 infection and preeclampsia was measured by an estimation of the pooled unadjusted and adjusted ORs with 95% CIs.

INTERVENTION (# IN THE GROUP): 15,524

COMPARISON (# IN THE GROUP): 775,430

FOLLOW UP PERIOD: Not applicable

RESULTS:

SARS-CoV-2 infection during pregnancy was associated with a statistically higher risk of:

- Preeclampsia (with and without severe features) (26 studies; N=786,861; OR 1.6; 95% CI, 1.5–1.8)
- Preeclampsia with severe features (7 studies; N=11,019; OR 1.8; 95% CI, 1.2–2.6)
- Eclampsia (3 studies; N= 407,519; OR 2.0; 95% CI, 1.0–3.8)
- HELLP syndrome (1 study; N= 406,446; OR 2.1; 95% CI, 1.4–3.0)

No significant difference in odds of preeclampsia without severe features was identified between pregnant women with COVID-19 infection and those without (5 studies; N= 6,926; OR 1.3; 95% CI, 0.81–1.9).

LIMITATIONS:

- This review included studies that did not require positive laboratory testing to confirm COVID-19 infection which could complicate the data.
- Most studies did not specify the temporality of outcome or the association between severity of condition and outcome, so the data on causality is not strong.
- Only 50% of the included studies controlled for potential confounding factors.

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Platelet-Rich Plasma for Tendinopathy: Benefit or Not?

Efficacy of Platelet-Rich Plasms Versus Placebo in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Trials

Dai W, Yan W, Leng X, et al. Efficacy of Platelet-Rich Plasma Versus Placebo in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Trials [published online ahead of print, 2021 Aug 2]. *Clin J Sport Med. 2021;* 10.1097/JSM.0000000000000961. doi:10.1097/JSM.0000000000000961

KEY TAKEAWAY: Injection of platelet-rich plasma is not superior to placebo at reducing pain or improving functional status in patients with tendinopathy at 4-6 weeks, 12 weeks, or >24 weeks.

STUDY DESIGN: Meta-analysis of 13 RTCs

LEVEL OF EVIDENCE: STEP 2 (downgraded due to bias, heterogeneity, and inconsistent blinding)

BRIEF BACKGROUND INFORMATION: Tendinopathy accounts for a significant portion of all musculoskeletal complaints. The most common treatment option, glucocorticoid injection, offers moderate short-term pain relief. However, it does not improve or resolve tendinopathy in the long-term. Regenerative therapies, such as platelet-rich plasma, have shown some potential to promote tendon healing in lab studies and small clinical trials, however their benefit has not been well supported in larger controlled trials.

PATIENTS: Patients with tendinopathy

INTERVENTION: Injection of autologous platelet-rich plasma at the site of tendinopathy

CONTROL: Placebo (saline injection, dry needling, or no treatment)

OUTCOME: Pain severity and functionality at 12 weeks
Secondary Outcomes: Pain severity and functional status at 4-6 weeks and >24 weeks

METHODS (BRIEF DESCRIPTION):

- A systematic literature search was performed to identify RCTs evaluating the efficacy of PRP vs placebo for treating tendinopathy in the following databases: MEDLINE, Embase, Scopus, SINAHL, Cochrane Library, and ClinicalTrials.gov.
- RCTs were selected that included patients diagnosed with tendinopathy of any type, PRP injection as the intervention, and saline, dry needling, or no intervention as the control.
- Data collected from these RCTs included number of participants, age, sex, BMI, type of tendinopathy (Achilles, patellar, rotator cuff, or lateral epicondylitis), intervention including method of administration, duration of follow-up, and outcomes.
- The outcomes of change in pain severity over time was measured using multiple different pain scales across the RCTs. Additionally, the visual analog scale (VAS) was used to verify the reliability of the conclusions made in these RCTs. The VAS scale is a validated subjective measure of acute and chronic pain. The scale is 0-100 with the higher numbers indicating worse pain.
- The outcome of change in function over time was measured in these RCTs by any objectively measurable aspect of function including strength and range of motion.

INTERVENTION (# IN THE GROUP): 287
COMPARISON (# IN THE GROUP): 289

FOLLOW UP PERIOD: The follow up periods were 4-6 weeks, 12 weeks, and >24 weeks.

RESULTS:

Pain Relief

- There was no significant difference in pain between PRP and control groups:
  - 4-6 weeks (MD 0; 95% CI, -0.90 to 0.99)
  - 12 weeks (MD 0.14; 95% CI, -0.79 to 1.1)
  - >24 weeks (MD -0.49; 95% CI, -1.9 to 0.69)

Function Improvement

- There was similar function improvement between PRP and placebo groups:
  - 4-6 weeks (SMD 0.11, 95% CI, -0.13 to 0.35)
  - 12 weeks (SMD 0.18, 95% CI, -0.13 to 0.49)
  - >24 weeks (SMD 0.26, 95% CI, -0.14 to 0.66)

LIMITATIONS:

- Seven of the included RCTs were determined to be low risk of bias, while six RCTs were determined to be at high risk of bias.
- Only seven of the RCTs included participants that were clearly blinded to the studies.
- In two of the RCTs the evaluators were not clearly blinded.
- One RCT was determined to have inadequate randomization.
- There was a moderate amount of heterogeneity among RCTs including differences in PRP

preparation and administration techniques, as well as among patients due to differences in age, sex, BMI, and level of physical activity.
- Type II statistical errors may have occurred because of an underpowered analysis.

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