GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 11 - 15, 2024

SPOTLIGHT: Magnesium Sulfate, Not Just for Asthma

Magnesium Sulfate, Not Just for Asthma

Magnesium Sulfate for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Ni H, Aye SZ, Naing C. Magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2022;5(5):CD013506. Published 2022 May 26. doi:10.1002/14651858.CD013506.pub2

KEY TAKEAWAY: The use of intravenous (IV) magnesium sulfate in acute chronic obstructive pulmonary disease (COPD) exacerbation shows efficacy in reducing hospital admissions, symptoms, and length of hospital stay.

STUDY DESIGN: Systematic review and meta-analysis of 11 randomized controlled trials (N=762)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Magnesium sulfate has been utilized for acute asthma exacerbations for its effect on smooth muscle relaxation resulting in bronchodilation and improved airway patency. Evidence is lacking for its use in other acute pulmonary conditions such as COPD. A systematic review was conducted to evaluate if a potential benefit exists for emergency department (ED) administration of IV and nebulized magnesium sulfate in cases of acute COPD exacerbation.

PATIENTS: Adults >35 years old

INTERVENTION: IV and/or nebulized magnesium sulfate + standard care

CONTROL: Placebo + standard care

PRIMARY OUTCOME: Hospital admissions, patients requiring non-invasive ventilation or endotracheal intubation, and symptoms

Secondary Outcome: Length of hospital stay

METHODS (BRIEF DESCRIPTION):

- Adults with a physician-diagnosed or guideline-based diagnosis of COPD who presented with an acute COPD exacerbation were included in the study.
- Patients with comorbidities including pneumothorax, bronchiectasis, other chronic lung diseases, or heart failure were excluded from the study.
- Interventions included:
  - IV magnesium sulfate (1.2–2.5 g infused over 15–20 min) + standard care
  - Nebulized magnesium sulfate (150 mg) + standard care
  - IV and nebulized magnesium sulfate
- The control group received placebo + standard care.
- Standard care consisted of nebulized ipratropium bromide (250–500 mg).
- Outcomes were measured by the rate of hospital admission, need for non-invasive ventilation or endotracheal intubation, length of hospital stay, and symptom scores.
- Symptom scores were measured by multiple validated scales including dyspnea severity score, Borg dyspnea score, and VAS dyspnea score.

INTERVENTION (# IN THE GROUP): 373

COMPARISON (# IN THE GROUP): 389

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- IV magnesium sulfate + standard care decreased hospital admission from the ED compared to placebo (3 RCTs, n=84; odds ratio [OR] 0.45; 95% CI, 0.23–0.88; I^2=0%).
- Nebulized magnesium sulfate + standard care shows no difference in the rate of hospital admission compared to placebo (1 RCT, n=109; OR 0.77; 95% CI, 0.21–2.8).
- IV magnesium sulfate + standard care reduced symptom scores compared to placebo + standard care (2 RCTs, n=101; mean reduction –1.4; 95% CI, –1.8 to –0.96; I^2=0%).
- There was no difference in the proportion of patients requiring non-invasive ventilation or endotracheal intubation between the groups (2 RCTs, n=107; OR 0.74; 95% CI, 0.31–1.8; I^2=0%).

Secondary Outcome –

- IV magnesium sulfate + standard care decreased the length of hospital stay compared to placebo + standard care (2 RCTs, n=54; mean difference –2.7 days; 95% CI, –4.7 to –0.66; I^2=0%).

LIMITATIONS:

- High heterogeneity of targeted outcomes in trials resulted in limited overlap in outcome data.

- The small sample size in each study resulted in a limited representation of each outcome included in the systematic review.
- Lack of follow-up limited the exploration of the potential effect of magnesium sulfate on recurrent COPD exacerbations.

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Are GLP-1RAs Safe and Effective to Combat Pediatric Obesity?

Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis

Ryan PM, Seltzer S, Hayward NE, Rodriguez DA, Sless RT, Hawkes CP. Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis. *J Pediatr.* 2021;236:137-147.e13. doi:10.1016/j.jpeds.2021.05.009

KEY TAKEAWAY: Glucagon-like peptide-1 receptor antagonists (GLP-1RA) in the pediatric population show a modest weight reduction, BMI, A1C, and blood pressure with nausea being the only statistically significant gastrointestinal side effect.

STUDY DESIGN: Meta-analysis of nine randomized control trials (N=574)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The prevalence of obesity in the pediatric population continues to rise in the United States. The recommendation for initial weight management involves multimodal lifestyle intervention. However, children are at risk of developing the metabolic consequences of obesity if these measures are unsuccessful. GLP-1RA has shown significant weight reduction and cardiovascular benefits in adults. This meta-analysis aims to address the safety profile and metabolic benefits in children.

PATIENTS: Obese children

INTERVENTION: Exenatide or liraglutide (GLP-1 RA)

CONTROL: Volume-matched placebo injector pens

PRIMARY OUTCOME: Weight reduction, improved cardiometabolic profile, and blood pressure

Secondary Outcome: Gastrointestinal treatment-emergent adverse events (TEAEs)

METHODS (BRIEF DESCRIPTION):

- Literature searches from Web of Science, PubMed/MEDLINE, and Scopus databases between January 1st, 1995, and January 1st, 2021 were included. Data extraction by two independent authors after initial screening for relevance and data reporting was completed by two independent working groups.
- Patients meeting BMI criteria for obesity (BMI >30 kg/m^2) with or without a history of type 2 diabetes (T2DM) or prediabetes were included in the study.
- Patients with type 1 diabetes, obesity-related genetic disorders, hypothyroidism, or eating disorder history were excluded from the study.
- Demographics:
  - Patient average age of 14 years old (+/- 2 years)
  - BMI 34–43 kg/m2
  - 53% of participants were female
  - The true number of T2DM or prediabetes participants is 34.5%
- All participants receiving exenatide reached 2 mg weekly or 10 mg daily dose.
- 70% of participants receiving liraglutide reached 1.8 mg weekly or 3.0 mg weekly maximal dosing, based on study guidelines.
- Patients receiving placebo received volume-matched injection doses once weekly.
- Primary outcomes were body weight, HbA1c, fasting glucose, total cholesterol, LDL, triglycerides, and systolic/diastolic blood pressure values.
- Secondary outcome measures were nausea, vomiting, diarrhea, abdominal pain, and elevated pancreatic enzymes.

INTERVENTION (# IN THE GROUP): 302

COMPARISON (# IN THE GROUP): 272

FOLLOW-UP PERIOD: 5–56 weeks

RESULTS:

Primary Outcome –

- Patients who received GLP-1RAs had a significant decrease in body weight compared to placebo (mean difference [MD] 1.5 kg; 95% CI, –2.5 to –0.5).
- Patients who received GLP-1RAs had a significant decrease in BMI compared to placebo (MD 1.2 kg/m2; 95% CI, –1.7 to –0.77).
- Patients who received GLP-1RAs had no difference in weight reduction benefits between liraglutide and exenatide (MD –1.1 kg; 95% CI, –1.7 to –0.55).
- Patients who received GLP-1RAs only demonstrated HbA1c reduction if there was preexisting T2DM or prediabetes (MD –1.1%; 95% CI, –1.9 to –0.18).

- Patients who received GLP-1RAs demonstrated systolic blood pressure reduction compared to placebo (MD –2.3 mmHg; 95% CI, –4.1 to –0.49).
- Patients who received a GLP-1RA had no reduction in fasting plasma glucose, lipid profiles, or diastolic blood pressure.

Secondary Outcome –

- The most common TEAEs were nausea, vomiting, and abdominal pain. Of these, only nausea was found to be statistically significant (relative risk [RR] 2.1; 95% CI, 1.4–3.1).
- Three liraglutide patients had mildly elevated lipase levels. One case of pancreatitis was identified.
- Other side effects from GLP-1 use identified were hypoglycemia and one case of elevated transaminases.

LIMITATIONS:

- Two studies contributed 134 and 251 respectively to the total of 574 participants.
- The sample size was small in seven studies (range 11–44).
- Two studies were open-label.
- There were high dropout rates in five of the nine studies.
- There was a short duration of <3 months in five of the nine studies.

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Exercise Is Medicine for Depressive Symptoms and Should Be Considered as First-Line Treatment

Exercise as Medicine for Depressive Symptoms? A Systematic Review and Meta-Analysis with Meta-Regression

Heissel A, Heinen D, Brokmeier LL, et al. Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. *Br J Sports Med.* 2023;57(16):1049-1057. doi:10.1136/bjsports-2022-106282

KEY TAKEAWAY: Supervised and group exercise of moderate intensity and aerobic exercise regimens may be effective in treating depression and depressive symptoms and should be considered by physicians in a patient-centered approach as a first-line, evidence-based treatment.

STUDY DESIGN: Systematic review and meta-analysis with meta-regression of 41 studies (n=2,264)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity)

BRIEF BACKGROUND INFORMATION: About 4.4% of the world's population live with a depressive disorder, a number that is worsening since the COVID-19 pandemic. It is the leading cause of disability worldwide. About 2/3 of adult patients do not receive adequate treatment, whether due to mental health stigma, refusal of psychotherapy, or intolerance to medication.

PATIENTS: Adults with depression

INTERVENTION: Exercise regimen

CONTROL: Non-exercise methods

PRIMARY OUTCOME: Mean change in depressive symptoms

METHODS (BRIEF DESCRIPTION):

- Databases were queried from inception to September 2022, and unpublished and ongoing trials from clinicaltrials.gov were searched.
- A total of 41 randomized control trials met inclusion criteria (21 studies assessing depressive symptoms and 20 with major depressive disorder).
- Studies using yoga, tai chi, or mind-body interventions were excluded in addition to studies that used other exercise interventions as a comparator.
- The percentage of females ranged from 26–100% with a mean age of 19–88 years old.
- Studies were performed in North America, South America, Europe, Asia and Australia.
- Exercise intervention was a planned, structured, repetitive, and purposive activity intended to improve or maintain physical fitness.
- The non-exercising control group included usual care, wait-list control conditions, or placebo pills.

INTERVENTION (# IN THE GROUP): 1,227

COMPARISON (# IN THE GROUP): 1,037

FOLLOW-UP PERIOD: 4–32 weeks

RESULTS:

Primary Outcome –

- Patients who participated in the exercise regimen had a significant improvement compared to those who received non-exercise treatments (1,227 vs 1,037, respectively; standard mean difference [SMD] –0.95; 95% CI, –1.2 to –0.71; I^2=83%).
  - Subgroup analyses showed a beneficial effect of exercise on depression regardless of depression classification, risk of bias, group exercise, sample size, and supervision by professionals.
- Patients with Major Depressive Disorder who participated in the exercise regimen had significant improvement compared to those who received non-exercise treatments (20 trials; SMD –0.098; 95% CI, –1.4 to –0.61; I^2=85%).

LIMITATIONS:

- The included studies were highly heterogeneous; however, the authors performed several subgroup analyses and meta-regressions to explore the sources.
- Many of the included studies had small sample sizes.
- The larger studies showed smaller but still similar results.
- Long-term effects could not be determined due to missing follow-up data.
- It was not possible to control for placebo effects due to the nature of the intervention.

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Looking at Prophylactic Antibiotics for Infants with Vesicoureteral Reflux

Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux

Morello W, Baskin E, Jankauskiene A, et al. Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux. *N Engl J Med.* 2023;389(11):987-997. doi:10.1056/NEJMoa2300161

KEY TAKEAWAY: Use of continuous prophylactic antibiotics in the first two years of life for infants with high-grade vesicoureteral reflux reduces the incidence of a first urinary tract infection (UTI), especially in females with grade IV or V reflux, but is associated with higher rates of antibiotic-resistant organisms.

STUDY DESIGN: Randomized, open-label, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinded study design and relatively small sample size)

BRIEF BACKGROUND INFORMATION: The current recommendation for infants with high-grade (III, IV, or V) vesicoureteral reflux (VUR) is to receive continuous antibiotic prophylaxis to prevent UTIs and potential kidney scarring. However, there is a lack of evidence supporting this recommendation and it is a controversial topic amongst treatment centers. Previous studies have assessed prophylaxis for infants with low-grade VUR and prior UTI, but have not evaluated this intervention for high-grade VUR in infants without a history of UTIs.

PATIENTS: Infants with high-grade VUR

INTERVENTION: Antibiotic prophylaxis

CONTROL: No antibiotic prophylaxis

PRIMARY OUTCOME: First symptomatic UTI

Secondary Outcome: Total UTIs, new kidney scarring, estimated glomerular filtration rate (eGFR), uropathogenic and antibiotic resistance pattern, serious adverse events

METHODS (BRIEF DESCRIPTION):

- Infants (1–5 months old) from 39 centers in Europe were recruited with vesicoureteral reflux grade III, IV, or V as indicated by imaging.
- Additional inclusion criteria included >35 weeks gestational age at birth and a glomerular filtration rate (GFR) >15 ml/min/m^2.
- Included participants were 78% male, 2.2% circumcised, 48% with bilateral VUR, and a median age of 3.4 months old.
- Exclusion criteria included previous UTI, posterior urethral valves, neurogenic bladder, or anatomical urinary obstruction.
- Participants were randomized in a 1:1 ratio to the prophylaxis group or the no-treatment group, with additional stratification based on current renal parenchymal damage.
- The choice of prophylactic antibiotic was based on local *E. coli* antibiotic resistance trends at the discretion of site investigators.
    - Infants in the treatment group received a once-daily dosing of one of the following antibiotics: Nitrofurantoin, amoxicillin-clavulanate, cefixime, or trimethoprim-sulfamethoxazole.
- Scheduled evaluations and monitoring for adherence or adverse events occurred at four, eight, 12, 18, and 24 months.
- The primary outcome was the incidence of the first symptomatic UTI.
    - Diagnosis of symptomatic UTI was based on the presence of acute symptoms, urinalysis findings of nitrites or leukocyte esterase, and positive urine culture of 10,000 colony-forming units (CFU) in a catheter sample or 100,000 CFU in a midstream sample.
- Secondary outcomes included the number of UTIs in two years, isolated organismal antibiotic resistance patterns, percentage of non-*E. coli* UTIs, and serious adverse events.

INTERVENTION (# IN THE GROUP): 146

COMPARISON (# IN THE GROUP): 146

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Antibiotic prophylaxis reduced the incidence of a first symptomatic UTI compared to no treatment (21% vs 36%, respectively; hazard ratio [HR] 0.55; 95% CI, 0.35–0.86, NNT=7).
- First UTI occurrence in the treatment group varied by gender, with most of the significant benefit occurring in females with grade IV or V reflux.

Secondary Outcome –

- Antibiotic prophylaxis resulted in fewer UTIs over two years of follow-up compared to no treatment

(60 vs 79 total UTIs; rate ratio [RR] 0.76; 95% CI, 0.59–0.97).

- Organisms isolated from participants in the prophylaxis group had a higher resistance rate to at least two antibiotics (52% vs 17%; RR 3.0; 95% CI, 1.5–5.9).
- Antibiotic prophylaxis also resulted in a higher percentage of non-*E. coli* UTIs, including *Pseudomonas* infections.
- No difference was found between groups in the number of infections requiring hospitalization or IV antibiotics, the incidence of new kidney damage, eGFR, or serious adverse events.

LIMITATIONS:

- The study participants were from varying countries with different bacterial resistance patterns.
- Infants were not provided the same prophylactic antibiotic.
- This study lacks a diverse racial representation since >95% of participants were White, which reduces generalizability.
- Infants with a previous UTI diagnosis were excluded from the study, however, this is often a major precursor to diagnosing vesicoureteral reflux in infants.
- The open-label study design introduces a risk of bias, mitigated by a well-defined objective primary outcome.

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When Things Get Out of Hand: Ketamine for Agitation

Rapid Agitation Control with Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial

Barbic D, Andolfatto G, Grunau B, et al. Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial. *Ann Emerg Med*. 2021;78(6):788-795. doi:10.1016/j.annemergmed.2021.05.023

KEY TAKEAWAY: In emergency department (ED) patients with severe agitation, intramuscular ketamine provided a significantly shorter time to adequate sedation than a combination of intramuscular midazolam and haloperidol. However, a study with greater power is needed to achieve confidence.

STUDY DESIGN: Randomized, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: There is a lack of protocol standardization for rapid sedation for acutely agitated patients in the ED. Benzodiazepines and antipsychotics are commonly used but pose concerning side effects. Ketamine may be a safer and more effective alternative.

PATIENTS: Adults with agitation

INTERVENTION: Ketamine

CONTROL: Midazolam + haloperidol

PRIMARY OUTCOME: Time to adequate sedation

Secondary Outcome: Need for rescue medications, adverse events, intubation, ICU admission

METHODS (BRIEF DESCRIPTION):

- Patients 19–60 years old, in the ED with severe psychomotor agitation defined by a Richmond Agitation Score of ≥3 were included in this study.
- Patients who had previously been enrolled, in police custody, pregnant, breastfeeding, or a known hypersensitivity, intolerance, or allergy to the medication were excluded.
- Patients were blinded and randomized to one of the following treatments:
  - 5 mg/kg of ketamine
  - 5 mg midazolam + 5 mg haloperidol
- Treatments were administered by ED providers who encountered a patient with agitation. Providers were blinded to the treatment.
- Agitation was measured using the Richmond Agitation Sedation Score (RASS) with scores ranging from –5 (no response to voice or physical stimulation) to +4 (violent, immediate danger to staff), with 0 being the baseline of alert and calm.
- Physicians ordered standardized testing for all patients including a complete blood count, electrolyte panel, serum toxicology, and electrocardiogram.
- Research assistants began observations five minutes after administration and recorded the RASS score in five-minute increments for 30 minutes.

INTERVENTION (# IN THE GROUP): 40

COMPARISON (# IN THE GROUP): 40

FOLLOW-UP PERIOD: 30 minutes

RESULTS:

Primary Outcome –

- Ketamine reduced the time to adequate sedation compared to midazolam + haloperidol (5.8 min vs 15 min; mean difference [MD] –8.8; 95% CI, –15 to –3.0).
- A greater proportion of patients receiving ketamine achieved adequate sedation at each five-minute time interval.

Secondary Outcome –

- There was no statistically significant difference in the proportion of patients who needed rescue medications.
- There was no statistically significant difference in the percentage of patients who experienced a serious adverse event.
- No patients in either arm needed intubation or ICU admission.

LIMITATIONS:

- The study was in one urban academic center.
- The targeted sample size was not reached due to COVID-19-mandated restrictions cutting the study short.
- Ketamine was only compared to a single-dose option of midazolam/haloperidol.

- Due to randomization results, a greater proportion of the ketamine arm were men and a greater proportion of the ketamine arm appeared to start the trial with more severe agitation.
- Patients were not closely monitored after the 30 minutes.

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