GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of May 1 - 5, 2023

SPOTLIGHT: SGLT2 Inhibitors Reduce Heart Failure-Related Hospitalizations in Non-Diabetics with Heart Failure

- Haldol for ICU Delirium?
- Are Migraines in Children and Young Teens Related to Anxiety and Depression?
- How Does Mental Health Impact the Treatment Outcome in Concussion Management?

SGLT2 Inhibitors Reduce Heart Failure-Related Hospitalizations in Non-Diabetics with Heart Failure

Sodium-glucose Cotransporter-2 Inhibitors in Patients with Heart Failure: A Systematic Review and Meta-Analysis

Zou X, Shi Q, Vandvik PO, et al. Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Heart Failure: A Systematic Review and Meta-Analysis. *Ann Intern Med*. 2022;175(6):851-861. doi:10.7326/M21-4284

KEY TAKEAWAY: Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors decrease hospitalizations for heart failure in patients with and without type 2 diabetes.

STUDY DESIGN: Meta-analysis of nine randomized controlled trials

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: SGLT2, an anti-diabetic drug, has cardiovascular benefits in patients with diabetes. Recent trials have shown the same is true in patients without diabetes. Compared to 2012, the projected medical costs in 2030 are expected to more than double due to heart failure hospitalizations. SGLT2 medications can help greatly reduce the burden of medical expenses in wider demographics than initially expected.

PATIENTS: Adult patients with heart failure and with or without type 2 diabetes

INTERVENTION: SGLT2 inhibitors

CONTROL: Placebo (one trial with sulfonylurea)

PRIMARY OUTCOME: Hospitalizations for heart failure (HF), all-cause mortality, kidney failure

Secondary Outcome: Diabetic ketoacidosis (DKA), genital infection, lower-limb amputation, bone fracture, cardiovascular (CV) death

METHODS (BRIEF DESCRIPTION):

- A comprehensive search was performed for RCTs that included:
  - Adults (mean age 62–75.7) diagnosed with heart failure (reduced or preserved ejection fraction) treated with SGLT2 inhibitors.
  - Included patients who had experienced hospitalization for HF, kidney failure, or death.
  - Treatment with SGLT2 inhibitors was compared to placebo (sulfonylurea in 1 trial).
  - Patients were enrolled whether or not they had diabetes mellitus.
  - Risk of DKA, genital infections, amputations, bone fracture, and CV death with SGLT2 inhibitors was compared to placebo.
  - The follow-up period was at least 24 weeks.

INTERVENTION (# IN THE GROUP): 8,118

COMPARISON (# IN THE GROUP): 8,740

FOLLOW-UP PERIOD: Six months to 26 months

RESULTS:

Primary Outcome –

- SGLT2 inhibitors reduced hospitalizations for heart failure compared to placebo.
  - ½ year: risk ratio (RR) 0.63 (95% CI, 0.53–0.75)
  - 1 year: RR 0.68 (95% CI, 0.58–0.80)
  - 2 years: RR 0.74 (95% CI, 0.60–0.90)
- SGLT2 inhibitors decreased hospitalizations for patients with and without type 2 diabetes compared to placebo.
  - With diabetes: RR 0.74 (95% CI, 0.61–0.91)
  - Without diabetes: RR 0.70 (95% CI, 0.50–0.96)
- SGLT2 inhibitors decreased hospitalizations regardless of the type of heart failure compared to placebo.
  - Reduced ejection fraction (EF): RR 0.72 (95% CI, 0.60–0.86)
  - Preserved EF: RR 0.73 (95% CI, 0.31–0.88)
- There were no significant differences in kidney failure or all-cause mortality at any interval with SGLT2 inhibitors compared to placebo.

Secondary Outcome –

- Genital infections were significantly greater in those treated with SGLT2 inhibitors compared to placebo (RR 2.7; 95% CI, 1.6–4.5).
- There was no significant difference in DKA, lower-limb amputation, bone fracture, or CV death.

LIMITATIONS:

- The chronicity of the presence of HF could affect the benefits of the medication.
- Short-term trials were not included.
- The longest follow-up was 26 months whereas longer trials could show fewer benefits or problems related to the drug.

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Haldol for ICU Delirium?

Haloperidol for the Treatment of Delirium in ICU Patients

Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Haloperidol for the Treatment of Delirium in ICU Patients. *N Engl J Med*. 2022;387(26):2425-2435. doi:10.1056/NEJMoa2211868

KEY TAKEAWAY: Haloperidol treatment does not lead to a significantly greater number of days alive and out of the hospital at 90 days compared to placebo.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Haloperidol is frequently used to treat delirium in ICU patients, but its use is not supported by practice guidelines. This study sheds light on composite outcomes of haloperidol use in ICU patients.

PATIENTS: ICU patients with delirium

INTERVENTION: Haloperidol

CONTROL: Isotonic saline

PRIMARY OUTCOME: Number of days alive and out of the hospital at 90 days

Secondary Outcome: Number of days alive without delirium or coma

METHODS (BRIEF DESCRIPTION):

- ICU patients with delirium who were 18 years old or older who were screened by either the CAM-ICU or ICDSC evaluations for delirium were included.
- Patients were blinded and randomized to one of the following treatments:
  - Intravenous haloperidol 2.5 mg three times daily
    - At the discretion of clinicians, more haloperidol could be given up to 20 mg daily. In cases of uncontrollable delirium, rescue medications such as propofol, benzodiazepines, or alpha-2 agonists could also be used. Other antipsychotics were not allowed.
  - The control group with delirium received 0.5 mL of isotonic saline three times daily.
- Primary outcome: number of days alive and out of the hospital within 90 days
- Secondary outcome: number of days alive without delirium or coma using the Richmond Agitation-Sedation Scale, the Ramsay Sedation Scale, the Motor Activity Assessment Scale, or the Glasgow Coma Scale

INTERVENTION (# IN THE GROUP): 510

COMPARISON (# IN THE GROUP): 490

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Haloperidol use did not result in a greater number of days alive and out of the hospital compared to placebo. (median score 35.8 vs 32.9 days, respectively).

Secondary Outcome –

- Haldol group had 5.1% (95% CI: -1.2 to 11.3) greater number of days alive without delirium or coma and 4.0% (95% CI: -2.2 to 10.1) greater in the number of days alive without mechanical ventilation compared to placebo group, although these findings were not statistically significant.

LIMITATIONS:

- Low number of patients from international sites may limit the generalization of data.
- Screening by clinical staff may leave out some eligible patients, including those with hypoactive delirium compared to hyperactive delirium.
- No data of other sedatives, pain medications, or nonpharmacologic interventions administered to the patient.

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Are Migraines in Children and Young Teens Related to Anxiety and Depression?

Anxiety and Depressive Symptoms and Disorders in Children and Adolescents with Migraines: A Systematic Review and Meta-Analysis

Falla K, Kuziek J, Mahnaz S, Noel M, Ronksley P, Orr S. Anxiety and Depressive Symptoms and Disorders in Children and Adolescents with Migraines: A Systematic Review and Meta-analysis. *JAMA Pediatrics*. 2022; 176 (12): 1176-1187. doi: 10.1001/jamapediatrics.2022.3940

KEY TAKEAWAY: Children and adolescents who present with migraines have more symptoms of depression and anxiety compared with healthy controls. As such, consider screening them for anxiety and depression.

STUDY DESIGN: Systematic review and Meta-analysis of 80 observational studies including case-control, cohort, and cross-sectional studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to low quality studies with significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Migraine is a worldwide disabling disease, and in children, there are hypotheses that it may be associated with internalization of symptoms - defined as an individual's tendency to react to stress with internal processes (anxiety and depression). This systematic review and meta-analysis aims at estimating the association between anxiety and depressive symptoms and disorders and migraines in children and adolescents and the magnitude of the relationship if any.

PATIENTS: Children and adolescents

INTERVENTION: Anxiety or depression

CONTROL: No anxiety or depression

PRIMARY OUTCOME: Diagnosis of migraine

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature review on the incidence of migraine among children and adolescents was done with 17,778 records identified and 4,946 studies screened.
- 80 studies were retained following eligibility assessment and included in the reviews.
- Eligibility criteria for study selection were as follows:
  - Children and adolescents 18 years or younger
  - Studies in which any spectrum of anxiety and depressive symptoms and disorders as defined by DSM-V were assessed.
- Studies reporting raw data on the association between internalizing symptoms, anxiety/depression symptoms or disorders, and migraine were pooled together (51 studies) in a meta-analysis using standard mean differences (SMD) or odds ratio (OR) with 95% Confidence Intervals (CIs).
- Of these 51 studies, 2 were cross-sectional studies, 28 were case-control and 2 were cohort studies.
- Estimates of the association between internalizing symptoms or disorders and migraine were generated.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied between one month to eight years

RESULTS:

Primary Outcome –

- The odds of having migraines were higher in children with:
  - Anxiety disorders (15 studies; OR 1.9; 95% CI, 1.5–2.5)
  - Depressive disorders (18 studies; OR 2.0; 95% CI, 1.5–2.8)
  - Depressive symptoms (17 studies; SMD 0.67; 95% CI, 0.46–0.87)
  - Anxiety symptoms (16 studies; SMD 1.1; 95% CI, 0.64–1.6)

LIMITATIONS:

- Results from the systematic review looked at exposure outcomes. Studies were of low quality with significant between-study heterogeneity and discrepant findings compared to the studies in the meta-analysis, so conclusions could not be reached.
- There were no reports on the number of subjects included in the meta-analysis.
- Studies were very heterogenous with regards to assessment and outcomes.
- Outcomes from the meta-analysis and systematic review had discrepancies among outcomes. The meta-analysis found an association between migraine and anxiety while the systematic review found no association.

- Most of the analyzed studies reported only unadjusted associations, thereby increasing the risk of bias due to unmeasured confounders.

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How Does Mental Health Impact the Treatment Outcome in Concussion Management?

Factors Associated with Additional Clinic Visits in the Treatment of Sports-Related Concussion: A Retrospective Cohort Study

Hou BQ, Yengo-Kahn AM, Hajdu K, et al. Factors Associated with Additional Clinic Visits in the Treatment of Sports-Related Concussion. *Clin J Sport Med*. 2022;32(6):588-594. doi:10.1097/JSM.0000000000001057

KEY TAKEAWAY: Patients that suffer sports-related concussions (SRC) may require multiple clinic visits before being discharged to the care of their athletic trainers (AT) based on several factors.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: This study helped evaluate the variables associated with the post-care management of athletes following an initial concussion, the factors limiting early recovery, and factors that may potentially cause repeat injuries.

PATIENTS: Patients with sports-related concussion

INTERVENTION: Further clinical management before AT

CONTROL: AT management

PRIMARY OUTCOME: Factors associated which needed further clinical management

METHODS (BRIEF DESCRIPTION):

- The study participants included patients aged 12–23-year-old that suffered a sports-related concussion.
- The study excluded 980 patients, including participants suffering from repeat concussions, those lost to follow-up at the clinic, and patients that did not necessitate discharge to AT.
- A small cohort of multidisciplinary providers, including sports medicine, orthopedics, neurosurgeon, and neurophysiologist, saw the patients in a controlled clinic to limit variabilities in their reporting methods.
- Patient data was compiled using manual chart extractions from the provider notes and inputted into the electronic research data capture database.
- Patients were excluded from the study if they did not fall within the study parameters, including the age range of patients, time of presentation, mode of injury, and positive head imaging findings.
- Patients reported the severity of their injury using the post-concussion symptom scale (PCSS) questionnaire during their initial visit.
- Patients self-reported their symptom severity quantitatively using the PCSS questionnaire scale that rated each of the twenty-two-point symptoms on a scale from 0 (no symptoms) to 6 (severe).
- The total points for each patient were calculated after completing the PCSS questionnaire to estimate an overall severity index.
- The overall statistical analysis of the study was calculated using the SPSS tool with an internal consistency score estimated at 0.93.
- The providers used the ICD code system in making a positive concussion diagnosis, following guidelines provided by the Concussion in Sport Group definition.
- Following the initial visit, providers decided on early discharge to an athletic trainer (AT) or a return to the clinic for ongoing management using a binary logistic regression evaluation too.

INTERVENTION (# IN THE GROUP): 288

COMPARISON (# IN THE GROUP): 236

FOLLOW-UP PERIOD: Through discharge

RESULTS:

Primary Outcome –

- Patients with a history of psychiatric disorders required additional clinic visits (Odds Ratio [OR] 3.1; 95% CI, 1.5–6.3).
- Patients with prior history of concussion required additional clinic visits (OR 1.4; 95% CI, 1.02–1.9).
- Patients with significantly higher PCSS scores at the initial visit required additional clinic visits (OR 1.1; 95% CI, 1.03–1.1)
- Younger athletes needed additional clinic visits (OR 0.87; 95% CI, 0.77–0.98).

LIMITATIONS:

- Given the requirements used in the exclusion criteria, it only included a small subset of individuals in the study.
- It needed AT involvement to measure the different periods between athletes' recovery processes.

- Different providers limited standardization of care regarding concussion management.
- Lack of access to athletic trainers in some schools prevented accurate data collection, affecting the decision for an earlier discharge.
- There were limited appropriate return-to-play protocols for athletes, potentially increasing the chance of repeat injuries or suffering long-term unfavorable effects of early return-to-play protocols.

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