GEMs of the Week

Volume 4 - Issue 3

GEMs
GOOD EVIDENCE MATTERS

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What's in this week's issue?

Week of January 15 - 19, 2024

SPOTLIGHT: Sports After 60 - Does it Keep the Pep in Your Step?

Sports After 60: Does it Keep the Pep in Your Step?

Effect of Sport on Health in People Aged 60 Years and Older: A Systematic Review with Meta-Analysis

S Oliveira J, Gilbert S, Pinheiro MB, et al. Effect of sport on health in people aged 60 years and older: a systematic review with meta-analysis. *Br J Sports Med.* 2023;57(4):230-236. doi:10.1136/bjsports-2022-105820

KEY TAKEAWAY: Sports may have promise for improving health outcomes in people aged 60 years old or older in the domains of cardiorespiratory fitness, physical function, mental health, and reducing fat mass. There remains uncertainty in its effect on strength, balance, lean mass, and bone mineral density.

STUDY DESIGN: Systematic review with meta-analysis of nine randomized controlled trials (N=628)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The number of people over 60 years old worldwide is expected to reach two billion by 2050. The WHO endorses regular physical activity as a proven way to combat conditions like diabetes, heart disease, and stroke, recommending 150–300 minutes of moderate intensity, or 75–100 minutes of vigorous-intensity aerobic physical activity per week for all adults. Sport is a fun recreational activity that may be an appealing option for older people to be physically active.

PATIENTS: Adults aged 60 years old and older

INTERVENTION: Any type of sport

CONTROL: No intervention or usual care

PRIMARY OUTCOME: Domains of physical activity, physical functioning, cognitive and emotional functioning, well-being, quality of life, and adverse events

METHODS (BRIEF DESCRIPTION):

- The study included RCTs with adults aged 60 years old or older, or with a mean age of at least 60 years old.
  - Participants could be from the general population or have a clinical condition as criteria for their inclusion.
- The majority of trials were conducted in high-income countries.
- Sports were conducted in community and clinical settings and included soccer, handball, floorball, and golf.
- Interventions were participation in any sport, involving physical exertion, skill, and/or coordination.
- Comparison groups were non-active controls or usual care.
- Outcome domains from a previously reported framework included physical functioning (cardiorespiratory fitness, balance, strength, body composition, and bone mineral density), cognitive and emotional functioning, well-being, and quality of life, through both quantitative and qualitative assessments.
- Excluded measurements included laboratory studies or biomarkers.
  - Social functioning was not assessed.
- The quality assessment of the evidence was determined by 11-item PEDro scores for methodologic quality and the GRADE system for evidence certainty rating (for outcomes with at least three trials).

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 12–52 weeks

RESULTS:

Primary Outcome –

- Sports had a small significant effect on cardiorespiratory fitness (expired gas analysis) compared to no intervention or usual care (5 trials, N=224; mean difference [MD] 2.1 mL kg/min; 95% CI, 0.89–3.3).
- Sports had a medium significant effect on physical function (sit-stand test or survey) compared to no intervention or usual care (4 trials, N=314; effect size 0.62; 95% CI, 0.05–1.2).
- Sports had a significant effect on reducing fat mass compared to no intervention or usual care (6 trials, N=361; MD –0.99; 95% CI, –1.8 to –0.23).
- Sports had a small significant effect on cognitive and emotional functioning (geriatric depression scale) compared to no intervention or usual care (2 trials, N=306; effect size 0.28; 95% CI, 0.06–0.51).

- There was no significant difference found in the effect of sport on overall physical activity participation, balance, strength, lean mass, bone mineral density, or quality of life.
- The majority of adverse events were minor sports-related injuries (average incidence 249 injuries per 1000 hours of exposure).

LIMITATIONS:

- Studies evaluated only short-term or immediate impacts of sports, thus sustainability and long-term effects remain unclear.
- Authors only considered publications in English, which may introduce bias.
- The inclusion of studies with both healthy participants and people with clinical conditions creates potential statistical heterogeneity.
- A limited range of sport types was studied (56% of trials and 73% of publications analyzed soccer).
- Limited number of studies overall, particularly evaluating quality of life, balance, and physical activity.

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2 Many Benefits from Sodium-Glucose Cotransporter Inhibition

Effect of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular and Kidney Outcomes- Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

Salah HM, Al'Aref SJ, Khan MS, et al. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-Systematic review and meta-analysis of randomized placebo-controlled trials. *Am Heart J.* 2021;232:10-22. doi:10.1016/j.ahj.2020.10.064

KEY TAKEAWAY: SGLT2 inhibitors improve cardiovascular and kidney outcomes regardless of pre-existing heart failure, diabetes, or kidney disease status.

STUDY DESIGN: Meta-analysis of eight placebo-controlled randomized controlled trials (N=59,747)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: SGLT2 inhibitors have shown significant promise in the treatment of diabetes as well as for their cardioprotective and renoprotective effects. However, the magnitude of this benefit remains nebulous, especially in the context of much heterogeneity among previously completed randomized controlled trials regarding cardiovascular and kidney outcomes.

PATIENTS: Elderly patients with varying chronic disease statuses

INTERVENTION: Addition of an SGLT2 inhibitor

CONTROL: Placebo

PRIMARY OUTCOME: Mortality, cardiovascular (CV) or composite kidney outcomes

METHODS (BRIEF DESCRIPTION):

- Individuals with a combination of multiple medical co-morbidities including diabetes mellitus, chronic kidney disease, and congestive heart failure were included in this study.
- RCTs were all randomized 1:1 to SGLT2i or placebo.
- Hazard ratios with confidence intervals were measured for all-cause mortality, CV mortality, hospitalization for heart failure (HHF), myocardial infarction (MI), stroke, and composite kidney outcomes (end-stage renal disease, doubling serum creatinine, or kidney-related mortality) over a mean follow-up period of >2.5 years.
- Subgroup analyses of aforementioned outcomes for varying combinations of the presence or absence of diabetes mellitus, chronic kidney disease, and congestive heart failure that included adverse outcome measures.

INTERVENTION (# IN THE GROUP): 33,153

COMPARISON (# IN THE GROUP): 26,594

FOLLOW-UP PERIOD: Mean 2.6 years

RESULTS:

Primary Outcome –

- Use of SGLT2i reduced the risk of:
  - All-cause mortality (hazard ratio [HR] 0.84; 95% CI, 0.78–0.91)
  - CV mortality (HR 0.84; 95% CI, 0.76–0.93)
  - HHF (HR 0.69; 95% CI, 0.64–0.74)
  - MI (HR 0.91; 95% CI, 0.84–0.99)
  - Composite kidney (HR 0.62; 95% CI, 0.56–0.70)
- There was no significant effect seen for stroke reduction.
- All above measures remained unchanged after subgroup analysis, however, the benefits of risk of MI did demonstrate some variability depending on the co-morbidity burden.
- SGLT2i increased the risk of diabetic ketoacidosis (odds ratio [OR] 2.9; 95% CI, 1.4–5.9) and genitourinary infections (OR 3.9; 95% CI, 3.01–5.2) compared to placebo.

LIMITATIONS:

- Variability existed amongst subgroup data between studies as well as broad variability between analyses.
- The data presented is summary data rather than patient-level outcome data.
- Some subgroup data was absent for certain trials and not included in the analysis.

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The Efficacy and Safety of Opioids in Acute Low Back and Neck Pain

Opioid Analgesia for Acute Low Back Pain and Neck Pain (The OPAL Trial): A Randomized Placebo-Controlled Trial

Jones CMP, Day RO, Koes BW, et al. Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomized placebo-controlled trial [published correction appears in Lancet. 2023 Aug 19;402(10402):612]. *Lancet*. 2023;402(10398):304-312. doi:10.1016/S0140-6736(23)00404-X

KEY TAKEAWAY: Opioids prescribed for acute low back or neck pain do not improve pain and are also associated with a significant risk of long-term misuse. Therefore, consideration must be given before opioids are prescribed in these conditions.

STUDY DESIGN: Triple-blinded, placebo-controlled randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Despite opioid analgesics only being recommended for the treatment of acute low back or neck pain when other treatments have failed, they are often prescribed as first-line treatment. There has not been substantial evidence supporting the efficacy or safety of opioids in this situation, and there has never been a placebo-controlled trial in this situation without the use of another pain medication before this study.

PATIENTS: Adults with low back pain and/or neck pain

INTERVENTION: Oxycodone-naloxone

CONTROL: Placebo

PRIMARY OUTCOME: Pain

Secondary Outcome: Adverse events, risk of misuse

METHODS (BRIEF DESCRIPTION):

- The study was conducted at 157 medical facilities in Sydney, NSW, Australia between 2016–2022.
- Participants were adults who presented to primary care clinics or emergency departments with moderate to severe pain for 12 weeks or less with at least one month of no pain beforehand.
    - Exclusion criteria: Known or suspected spinal pathology (such as fracture or cauda equina syndrome), spinal surgery within the past six months or planned during the treatment period, and use of opioid analgesics at a dose higher than 15 mg of oral morphine equivalent per day for more than five days.
- The opioid group started at 5 mg oxycodone/2.5 mg naloxone by mouth twice a day.
    - Naloxone was prescribed to minimize the side effects of constipation and unmasking of the treatment group.
    - Dosing was titrated to a maximum of 10 mg oxycodone twice a day.
    - Treatment continued until improvement which was defined as a pain score of 0–1 out of 10 for three consecutive days or a maximum of six weeks.
- Guideline-recommended care was provided to both groups, including reassurance of a positive prognosis, advice to remain active, and if necessary other treatments including non-opioid analgesics.
- Outcomes were measured according to pain intensity by a 0–10 Brief Pain Inventory Pain Severity Subscale (BPI-PS), with a higher score indicating a greater amount of pain.

INTERVENTION (# IN THE GROUP): 174

COMPARISON (# IN THE GROUP): 173

FOLLOW-UP PERIOD: Six, 12, and 52 weeks

RESULTS:

Primary Outcome –

- There was no significant difference in pain between the two groups at:
    - The end of the six-week treatment period (mean difference [MD] 0.53; 95% CI, –0.00 to 1.1)
    - 12-week follow-up: (MD 0.48; 95% CI, –0.06 to 1.0)
- There was a small but significant difference in pain at 52 weeks favoring the placebo group (MD 0.57; 95% CI, 0.02–1.1).
- When back pain was isolated at six weeks there was a difference in pain score favoring the placebo group (MD 2.3; 95% CI, 0.55–4.1).

Secondary Outcome –

- There was no significant difference in adverse events reported between the treatment and placebo group.

- There was a higher risk of misuse in the opioid treatment group at 52 weeks follow-up (20% in the treatment group vs 10% in placebo, *p*=.5).

LIMITATIONS:

- There was no monitoring of other guideline-recommended care given to the patients throughout the trial, including the use of other non-opioid analgesics.
- The pain scale (BPI-PS) was self-reported and therefore introduced bias and subjectivity.
- 25% of the treatment group and 20% of the placebo group had a protocol deviation (taking an opioid before randomization or other opioid use).

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App-Based Cognitive Behavioral Therapy- Does It Really Work for Pregnant Women?

The Preventative Effect of Internet-Based Cognitive Behavioral Therapy for Prevention of Depression During Pregnancy and in the Postpartum Period (iPDP): A Large Scale Randomized Controlled Trial

Nishi D, Imamura K, Watanabe K, et al. The preventive effect of internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum period (iPDP): a large scale randomized controlled trial [published correction appears in Psychiatry Clin Neurosci. 2023 May;77(5):304]. *Psychiatry Clin Neurosci.* 2022;76(11):570-578. doi:10.1111/pcn.13458

KEY TAKEAWAY: Internet-based cognitive behavioral therapy (CBT) does not affect the onset of new major depressive episodes (MDEs) in the postpartum period when compared with placebo.

STUDY DESIGN: Two-arm, parallel-group, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: An estimated 17% of postpartum women are diagnosed with postpartum depression (PPD) worldwide. Antenatal CBT is recommended as the most effective way to prevent PPD, however, few studies have investigated internet-based CBT.

PATIENTS: Pregnant patients

INTERVENTION: Internet-based CBT

CONTROL: Placebo

PRIMARY OUTCOME: Incidence of MDE

Secondary Outcome: Depression symptom scores

METHODS (BRIEF DESCRIPTION):

- Most patients were employed (70.8%) and nearly half had completed a university degree (45.5%).
- Inclusion criteria:
  - Primiparous and multiparous women who were at least 20 years old (mean age 30.44 years old)
  - Had a Luna Luna Baby application user ID
  - At 16–20 weeks gestation (mean 16.98 weeks)
- Exclusion criteria:
  - History of MDE or bipolar disorder
- Patients were randomized to one of the following groups:
  - Intervention: Six modules on the Luna Luna Baby app based on CBT were presented once per week for five minutes and given general information about mental health during pregnancy.
  - Control: General information about mental health during pregnancy was available when opening the Luna Luna Baby app.
- The incidence of MDE by 32 weeks gestation and three months postpartum was measured using the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) 3.0.
- Depression symptom scores were measured at one week postpartum using two scales:
  - Edinburgh Postnatal Depression scale (EPDS) scores (10 items on a 4-point scale with a total score range 0–30, 30 being most severe).
  - Kessler's Psychological Distress Scale (K6) scores (six items to assess psychological distress during the past 30 days, on a 5-point scale, total score 0–24, with higher scores indicating more distress, a score of four or less was considered low distress for this study).

INTERVENTION (# IN THE GROUP): 2,509

COMPARISON (# IN THE GROUP): 2,508

FOLLOW-UP PERIOD: Three months postpartum

RESULTS:

Primary Outcome –

- There was no significant difference in the incidence of MDE between the intervention (internet-based CBT) and the control (placebo) groups (intervention 2.35% vs control 2.91%; hazard ratio [HR] 0.85; 95% CI, 0.61–1.20).

Secondary Outcome –

- There was no significant difference in depression symptom scores between the two groups.

LIMITATIONS:

- All data was self-reported to include pregnancy status and gestational age, which limited the strength of the study due to a lack of laboratory and ultrasound confirmation.

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Azithromycin vs Beta Lactams for COPD Exacerbations

Azithromycin Versus Beta-Lactams in Hospitalized Patients with Acute Exacerbations of COPD

Baalbaki N, Giuliano C, Hartner CL, Kale-Pradhan P, Johnson L. Azithromycin Versus Beta-lactams in Hospitalized Patients with Acute Exacerbations of COPD. *J Gen Intern Med.* 2022;37(16):4183-4188. doi:10.1007/s11606-022-07486-5

KEY TAKEAWAY: Azithromycin may be superior to beta lactams for COPD exacerbations.

STUDY DESIGN: Retrospective, observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Acute exacerbations of chronic obstructive pulmonary disease (COPD), associated with increased mortality/morbidity and high healthcare expenditure, are commonly treated with antibiotics, as 50% of exacerbations are caused by bacterial infection. However, there is limited evidence surrounding which antibiotic to use, despite judicious antibiotic use being more important than ever in the era of antibiotic resistance. This study compared azithromycin vs beta-lactams, as beta-lactams do not target atypical bacteria but have less resistance against *Strep pneumoniae*.

PATIENTS: Hospitalized patients with acute exacerbations of COPD

INTERVENTION: Azithromycin

CONTROL: Beta-lactams

PRIMARY OUTCOME: Treatment failure rate (composite endpoint)

Secondary Outcome: Length of stay and individual endpoints from a composite endpoint (in-hospital mortality, ICU admission, initiation of invasive mechanical ventilation, initiation of a new antibiotic, steroid therapy), or readmission due to AECOPD within 30 days of discharge

METHODS (BRIEF DESCRIPTION):

- Retrospective, multicenter cohort study across six hospitals in Michigan.
- Patients >18 years old hospitalized for acute exacerbation of COPD (AECOPD) were included in the study.
- Received at least two consecutive days of treatment with either azithromycin or a beta-lactam.
- The treatment failure rate was a composite of in-hospital mortality, admission to intensive care, initiation of invasive mechanical ventilation, initiation of a new antibiotic, steroid therapy escalation, or readmission due to AECOPD within 30 days.
- Patients were identified through an institutional database and data was obtained from electronic medical records.
- Logistic regression and propensity matching were used.

INTERVENTION (# IN THE GROUP): 428

COMPARISON (# IN THE GROUP): 167

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Beta-lactams were associated with an increased risk of treatment failure (OR 2.30; 95% CI, 1.5–3.6).

Secondary Outcome –

- Patients receiving beta-lactams had a higher incidence of requiring new antibiotics (12.6% vs 4.2%; $p<.001$) and of readmission within 30 days (19.3% vs 12.4%; $p=.03$).
- Patients receiving azithromycin had a shorter length of stay (3.9 vs 5 days; $p<.001$).
- Neither group had increased rates of antibiotic-associated diarrhea (1.4% in the azithromycin group vs 0.0% in the beta-lactam group; $p=.6$) or CDAD (0.5% in the azithromycin group vs 0.0% in the beta-lactam group; $p=1.00$).

LIMITATIONS:

- Observational, not randomized study.
- Beta lactams used were mostly ceftriaxone or cefuroxime which may limit generalizability.
- There is no information about the number of exacerbations in the past 90 days.
- More patients in the azithromycin group received long-acting inhalers at discharge.
- Steroid doses were higher than what the guidelines suggest.
- Many patients were excluded due to receiving both azithromycin and beta-lactams.

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