GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 4 - Issue 46

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of November 11 - 15, 2024

SPOTLIGHT:

ADHD Meds: Not Just for Focus, They Might Save Your Life

ADHD Meds: Not Just for Focus, They Might Save Your Life

ADHD Pharmacotherapy and Mortality in Individuals with ADHD

Li L, Zhu N, Zhang L, et al. ADHD Pharmacotherapy and Mortality in Individuals With ADHD. *JAMA*. 2024;331(10):850-860. doi:10.1001/jama.2024.0851

KEY TAKEAWAY: Initiation of attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy in individuals with ADHD is associated with lower all-cause mortality.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Initiation of medication in individuals with ADHD has concerns for premature mortality including increased cardiovascular risks. It is unknown if ADHD medication is influencing mortality risk. This study evaluated whether ADHD medication independently impacts mortality risk.

PATIENTS: Individuals with ADHD

INTERVENTION: Initiation of ADHD medication

CONTROL: Non-initiation of ADHD medication

PRIMARY OUTCOME: All-cause mortality and cause-specific mortality

METHODS (BRIEF DESCRIPTION):

- Data was obtained from Swedish national registries for all individuals 6–64 years old without current ADHD medication use in Sweden.
- The study group included individuals newly diagnosed with ADHD from 2007–2018 who had not previously taken ADHD medication.
- The treatment group included patients who initiated any of six ADHD medications, including methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, atomoxetine, and guanfacine, within three months of diagnosis.
- The comparison group included patients who were not treated with ADHD medication.
- Patients were followed for up to two years after ADHD diagnosis, death, emigration, or December 31, 2020, whichever came first.
- The primary outcome measured two-year all-cause and cause-specific mortality rates.
    - All-cause mortality included both natural and unnatural causes.
    - Cause-specific mortality was defined as natural causes (physical conditions) and unnatural causes (suicide, accidental poisoning, unintentional injuries).
- Results were adjusted for covariates to include demographics, psychiatric comorbidities, and other psychiatric medications.

INTERVENTION (# IN THE GROUP): 84,282

COMPARISON (# IN THE GROUP): 64,374

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- ADHD medication decreased the risk for all-cause mortality compared to unmedicated patients (adjusted hazard ratio [aHR] 0.79; 95% CI, 0.70–0.88).
- ADHD medication initiation did not have a significant impact on natural cause mortality compared to unmedicated patients (aHR 0.86; 95% CI, 0.71–1.1).
- ADHD medication decreased the risk of unnatural cause mortality compared to unmedicated patients (aHR 0.75; 95% CI, 0.66–0.86).

LIMITATIONS:

- The observational nature of the study does not take into account all confounding factors, most significantly the lifestyle of an individual.
- Other confounding factors were not observed such as access to non-medication treatment such as therapy/social support.
- Inability to measure medication compliance.
- Potential misclassification of cause of death and cause of death (natural vs unnatural).

Peter Choi, DO
NCC Family Medicine Residency
Fort Belvoir, VA

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 Air Force Medical Department, the Air Force at large, or the Department of Defense.

Cefepime vs Piperacillin-Tazobactam for Sepsis: The Debate Continues

Mortality of Patients with Sepsis Administered Piperacillin-Tazobactam vs Cefepime

Chanderraj R, Admon AJ, He Y, et al. Mortality of Patients With Sepsis Administered Piperacillin-Tazobactam vs Cefepime. *JAMA Intern Med*. 2024;184(7):769-777. doi:10.1001/jamainternmed.2024.0581

KEY TAKEAWAY: In patients with suspected sepsis, piperacillin-tazobactam (PTZ) is associated with a higher 90-day mortality compared to those treated with cefepime.

STUDY DESIGN: Single-center, retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Sepsis is a frequent cause of hospital admission and is associated with significant mortality. Conflicting data from recent trials have brought into question the most effective initial empiric antibiotic choice for treating sepsis. This study aimed to investigate the antibiotic selection for treating sepsis.

PATIENTS: Adults with undifferentiated sepsis

INTERVENTION: Vancomycin + piperacillin-tazobactam

CONTROL: Vancomycin + cefepime

PRIMARY OUTCOME: 90-day mortality

Secondary Outcome: Organ failure, ventilator use, vasopressor-use

METHODS (BRIEF DESCRIPTION):

- The inclusion criteria were:
  - Adults ≥18 years old who met sepsis surveillance criteria
  - Received empirical antibiotic treatment within the first 24 hours of presentation to the emergency department (ED)
  - Had blood cultures drawn in the first 24 hours
  - Had acute organ dysfunction in the first 24 hours
  - Received antibiotics for at least one day
- Exclusion criteria included:
  - Patients transferred from outside hospitals
  - Patients with clear indications for using anti-anaerobic antibiotics
- All patients with suspected sepsis were treated with vancomycin and either PTZ or cefepime.
- The primary outcome was mortality within 90 days of presentation identified via the Social Security Death Index.
- The secondary outcomes were organ failure-free days defined as days within the first 28 days post-ED arrival without the use of vasopressors, dialysis, or mechanical ventilation

INTERVENTION (# IN THE GROUP): 4,523

COMPARISON (# IN THE GROUP): 3,046

FOLLOW-UP PERIOD: 90 days since presentation to ED

RESULTS:

Primary Outcome –

- PTZ was associated with higher 90-day mortality compared to cefepime (absolute change 5.0%; 95% CI, 1.9–8.1).

Secondary Outcome –

- PTZ group had significantly more days with the following compared to cefepime:
  - Organ failure (absolute change 2.0 days; 95% CI, 1.4–2.7)
  - Ventilator use (absolute change 1.1 days; 95% CI, 0.58–1.6)
  - Vasopressor use (absolute change 1.5 days; 95% CI, 1.0–2.0)

LIMITATIONS:

- As a retrospective cohort study relying on electronic medical records, it is vulnerable to unobserved confounding.
- The findings of this single-center study may not be generalizable to other settings or populations.
- Information on dosing of PTZ as a prolonged infusion vs intermittent infusion was not provided.

Kaiyang Feng, DO
UAMS Southwest FMRP
Texarkana, AR

Hold the Heparin?

A More Selective vs A Standard Risk-Stratified, Heparin-Based, Obstetric Thromboprophylaxis Protocol

Champion ML, Blanchard CT, Lu MY, et al. A More Selective vs a Standard Risk-Stratified, Heparin-Based, Obstetric Thromboprophylaxis Protocol. *JAMA*. 2024;332(4):310-317. doi:10.1001/jama.2024.8684

KEY TAKEAWAY: Using a selective risk-stratified approach to anticoagulation in post-partum women is associated with reduced wound hematomas compared to the standard risk-stratified approach.

STUDY DESIGN: Retrospective observational study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The University of Alabama at Birmingham (UAB), in 2016, utilized a pregnancy-related venous thromboembolism (VTE) protocol based on the American College of Obstetricians and Gynecologists (ACOG) guidelines regarding heparin-based postpartum VTE prophylaxis. What was observed was an increased incidence of wound hematomas without a significant reduction of VTEs, and in response, a more selective risk-stratified algorithm was utilized in 2021. The objective of this study was to evaluate the outcomes of the two protocols.

PATIENTS: Post-partum patients

INTERVENTION: More selective risk-stratified protocol

CONTROL: Standard risk-stratified protocol

PRIMARY OUTCOME: Rate of wound hematoma

Secondary Outcome: Rate of new VTE diagnosis

METHODS (BRIEF DESCRIPTION):

- The University of Alabama at Birmingham collected data during an observation period for the original protocol from 2016–2018 and the selective protocol from 2021–2023.
- The patients included were pregnant patients giving birth at UAB.
- Exclusion criteria included patients already on outpatient anticoagulation (prior VTE or thrombophilia).
- The original risk-stratified protocol included initiating anticoagulation with enoxaparin if patients had two or more risk factors vs the more selective protocol required three or more risk factors for the patients to qualify for anticoagulation.
- Both protocols required anticoagulation if one major risk factor was present, such as prior VTE.
- Clinical outcomes were compared for patients who delivered during each protocol period and included superficial and deep hematomas, defined by their presence above or below the rectus fascia respectively
- Secondary outcomes included incidence of VTE up to six weeks postpartum
- Chi-squared/Fisher tests were used for categorical variables and T-tests/Wilcoxon rank-sum tests were used for continuous variables
- Patient characteristics were identified as statistically significant if they differed significantly between groups (P<0.25).

INTERVENTION (# IN THE GROUP): 5,059

COMPARISON (# IN THE GROUP): 12,430

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- The selective risk-stratified protocol was associated with a decrease in wound hematomas compared to the standard risk-stratified protocol (adjusted odds ratio [aOR] 0.38; 95% CI, 0.21–0.67).

Secondary Outcome –

- The selective risk-stratified protocol was associated with fewer wound complications compared to the standard risk-stratified protocol (aOR 0.66; 95% CI, 0.50–0.86).
- The selective risk-stratified protocol was not associated with the rate of VTE or time from delivery to VTE diagnosis.

LIMITATIONS:

- Could not evaluate causality or fully address confounding given the retrospective nature of the study
- The study involved a high-risk population that was more likely to experience wound complications

Louis Gerges, MD
IU Health Arnett FMRP
Lafayette, IN

Blood Flow Restriction Training: Does It Enhance Strength Gains in Athletes?

Rotator Cuff Training with Upper Extremity Blood Flow Restriction Produces Favorable Adaptations in Division IA Collegiate Pitchers: A Randomized Trial

Lambert BS, Hedt C, Ankersen JP, et al. Rotator cuff training with upper extremity blood flow restriction produces favorable adaptations in division IA collegiate pitchers: a randomized trial. *J Shoulder Elbow Surg*. 2023;32(6):e279-e292. doi:10.1016/j.jse.2023.02.116

KEY TAKEAWAY: Blood flow restricted (BFR) training with low-load resistance exercise (LIX) performed in tandem with an offseason pitching program increases lean shoulder mass and muscular endurance in the throwing arm while preserving pitching mechanics when compared to the same training routine without BFR in collegiate baseball pitchers.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size of elite-level athletes)

BRIEF BACKGROUND INFORMATION: Prior studies have shown that using BFR training in tandem with LIX significantly increases muscle hypertrophy and function, which can help to improve athletic training regimens. This study aimed to evaluate the effects of BFR-LIX training when applied specifically to collegiate pitchers.

PATIENTS: Division IA collegiate baseball pitchers

INTERVENTION: BFR training with 50% occlusion

CONTROL: Training without BFR

PRIMARY OUTCOME: Regional lean mass, rotator cuff strength and endurance

Secondary Outcome: Fastball mechanics

METHODS (BRIEF DESCRIPTION):

- The study was made up of 28 division IA collegiate baseball players from a single team with no contraindications to exercise and were actively participating in a team-led offseason training program.
- All athletes also participated in their normal off-season training program for eight weeks.
- Participants were randomized to the following treatment:
  - A BFR -LIX rotator cuff training program, with 50% arterial occlusion of the pitching arm was implemented biweekly directly following high-intensity training biweekly.
  - Both the BFR and Non-BFR groups completed the same four exercises during each of these sessions.
- For each exercise, all participants completed the same amount of sets and reps, taking the last set of each exercise to failure.
- Lean mass was evaluated using a Dual-energy X-ray absorptiometry (DEXA) scan the week before, and after eight weeks, and with at least 72 hours of rest before imaging.
- Isometric rotator cuff strengthening occurred during the same week as imaging but on a separate day.
  - Strength was assessed by a physical therapist in the rested state, with at least 72 hours of rest before assessment.
  - Peak strength was measured via a microFET2 hand-held dynamometer.
- Pitching biomechanics for 10 fastball throws were observed in a controlled indoor pitching lane with the Kinematics captured by a specialized motion capture system using Vicon's Nexus software for analysis.

INTERVENTION (# IN THE GROUP): 15

COMPARISON (# IN THE GROUP): 13

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- BFR increased lean shoulder mass compared to their baseline (mean increase 227±60 g; *P*<.001).
  - The No-BFR group showed no significant increase.
- BFR increased isometric strength for Internal rotation at 90° in the throwing arm compared to their pre-training strength (mean increase 2.4±2.3 kg; *P*=.041).
  - The No-BFR group showed no significant increase.
- BFR increased achievable workload in dumbbell scaption compared to baseline (mean increase 190±3.2kg; *P*=.005).

- No-BFR increased achievable workload in dumbbell scaption compared to baseline (mean increase 90±3.3 kg; *P*=.005).

Secondary Outcome –

- No-BFR improved fastball mechanics with greater external rotation at front foot contact (9.0°±7.9°; *P*=.028) and reduced forward (3.6°±7.9°; *P*=.001) and lateral (4.6°±3.4°; *P*=.007) tilt of the trunk when releasing the ball compared to baseline.
- The BFR group showed no significant changes in their pitching biomechanics compared to their baseline.

LIMITATIONS:

- The study had a relatively small sample size of 28 participants.
- The participants in the study were limited to elite college-level athletes from the same program, therefore limiting generalizability.

Robert Taylor, DO
Ocean University Medical Center FMRP
Brick, NJ

Moving Past the Pain: Managing Chronic Back Pain Through Exercise

Some Types of Exercise Are More Effective Than Others in People with Chronic Low Back Pain: A Network Meta-Analysis

Hayden JA, Ellis J, Ogilvie R, et al. Some types of exercise are more effective than others in people with chronic low back pain: a network meta-analysis. *J Physiother*. 2021;67(4):252-262. doi:10.1016/j.jphys.2021.09.004

KEY TAKEAWAY: Exercise therapies are not more effective than non-exercise treatments for reducing pain and functional limitations in people with chronic low back pain. The McKenzie method is not more effective than other exercise therapies for reducing pain and functional limitations in people with chronic low back pain.

STUDY DESIGN: Systematic review with network meta-analysis of 217 randomized controlled trials (N=20,969)

LEVEL OF EVIDENCE: STEP 4 (downgraded due to significant heterogeneity and bias)

BRIEF BACKGROUND INFORMATION: Current treatments for chronic low back pain include exercise, however, there was limited evidence to support one specific form of exercise program over another. This study assessed how primary care physicians can implement alternative exercise treatments for low back pain.

PATIENTS: Adults with chronic, non-specific low back pain

INTERVENTION: Exercise treatments

CONTROL: Various non-exercise treatments

PRIMARY OUTCOME: Pain intensity and functional limitations

METHODS (BRIEF DESCRIPTION):

- Adults with chronic, non-specific low back pain (duration ≥12 weeks) were included, with a mean age of 43–45 years old.
- There were 11 different exercise groups categorized into the following: McKenzie therapy, flexibility, functional restoration, core strengthening, mixed exercises, general strengthening, aerobic exercises, stretching, yoga, or other specific exercises.
- The exercise groups were compared to a variety of non-exercise treatments that were categorized into the following: Placebo, no treatment, or usual care; education; manual therapy; back school; electrotherapy; mixed physiotherapy; psychological therapy; analgesics; and relaxation.
- The primary outcome measured pain intensity and functional limitations:
  - Pain intensity was measured on a scale from 0–100 points with a decrease of ≥15 points considered to be clinically important pain reduction.
  - Functional limitation was also measured on a scale from 0–100 points, with a decrease of >10 points to be considered clinically significant difference in function.
- Short-term outcomes (6 to 12 weeks) were the primary focus.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (<6 weeks to >48 weeks)

RESULTS:

Primary Outcome –

- Exercise interventions failed to achieve clinically significant reductions in pain intensity compared to minimal intervention or to each other.
- The McKenzie method showed no clinically significant reduction of pain intensity when compared to:
  - Minimal intervention (8 studies, n=428; researchers found a mean difference [MD] of –15; 95% CI, –21 to –8.2)
  - Functional restoration (researchers observed an MD of 0.1; 95% CI, –8.3 to 8.6)
  - Pilates (researchers noted an MD of –3.9; 95% CI, –11 to 3.3)
  - Core strengthening (researchers calculated an MD of 1.4; 95% CI, –5.0 to 7.9)
- Exercise interventions did not produce clinically significant improvements in functional limitations compared to minimal intervention or each other.
- The McKenzie method showed no clinically significant improvement in functional limitations when compared to:
  - Minimal intervention (7 studies, n=419; researchers found an MD of –12; 95% CI, –17 to –7)

- Functional restoration (researchers observed an MD of 4.3; 95% CI, –1.9 to 11)
- Pilates (researchers noted an MD of 1.5; 95% CI, –4.1 to 7.2)
- Flexibility (researchers calculated an MD of –0.7; 95% CI, –8.5 to 7.1)

LIMITATIONS:

- The overall certainty of evidence for most treatment comparisons was judged to be low to moderate, primarily due to within-study risk of bias and heterogeneity.
- Despite exploring multiple populations, exercises, and methodological characteristics, unexplained heterogeneity remained, which decreased confidence in the available evidence.
- There was incomplete reporting of trial and population characteristics in some included studies.
- There were differing opinions about treatment type classifications and potential misclassification of exercise types and population characteristics.
- The authors noted that the interventions that appeared to be most effective were also the costliest to deliver and "purchase" for patients.
- Many of the direct meta-analyses had moderate to substantial statistical heterogeneity, as measured by the I^2 statistic.
- Egger's test suggested possible publication bias in some of the meta-analyses with ≥10 trials.

Dimitri Villanueva, MD
University of South Alabama FMRP
Mobile, AL

The Effect of Junk Food Consumption on Mental Health in Adults

Association Between Junk Food Consumption and Mental Health Problems in Adults: A Systematic Review and Meta-Analysis

Ejtahed HS, Mardi P, Hejrani B, et al. Association between junk food consumption and mental health problems in adults: a systematic review and meta-analysis. *BMC Psychiatry*. 2024;24(1):438. Published 2024 Jun 12. doi:10.1186/s12888-024-05889-8

KEY TAKEAWAY: Consistent junk food consumption is associated with depression and psychological stress in adults compared to minimal junk food consumption.

STUDY DESIGN: Systematic review and meta-analysis of seven longitudinal studies, nine cross-sectional studies, and one case study (N=159,885)

LEVEL OF EVIDENCE: STEP 4 (downgraded due to the design of included studies)

BRIEF BACKGROUND INFORMATION: The continual rise of depression and anxiety throughout the world has had a significant impact on the mental health and quality of life of adult populations. Many environmental factors have a known association with the development of mental health disorders. With the increasing consumption of junk foods, such as ultra-processed foods, fast foods, unhealthy snacks, and sugar-sweetened beverages, a possible link may also be present with this environmental factor. This study aimed to evaluate how junk food consumption may be associated with mental health disorders in adults.

PATIENTS: Adults

INTERVENTION: Consistent consumption of fast-food/ultra-processed food

CONTROL: Minimal consumption of junk food

PRIMARY OUTCOME: Mood disorders, mental health outcomes, and stress

METHODS (BRIEF DESCRIPTION):

- Included studies were conducted in France, Saudia Arabia, Brazil, Spain, the United States, China, Australia, the United Kingdom, and Iran in adults ≥18 years old.
- Studies looked at participants who consumed large portions of unhealthy/junk foods, including ultra-processed foods such as sweets, snacks, sodas, artificial additives, high-fat content, frozen foods, canned foods, microwavable foods, and processed meats.
- The comparison group included participants who consumed minimal amounts of the junk foods mentioned above.
- The results were pooled using a random effects analysis.
- Studies looked at the mental health status of those who consumed large quantities of junk food and compared these individuals to those who consumed minimal amounts of junk food.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Cross-sectional studies:
  - Junk food consumption was associated with increased stress compared to minimal junk food consumption (4 studies, n=13,500; odds ratio [OR] 1.3; 95% CI, 1.0–1.6; I^2=74%).
  - Junk food consumption was associated with higher rates of depression compared to minimal junk food consumption (6 studies, n=74,127; OR 1.2; 95% CI, 1.0–1.3; I^2=66%).
- Cohort studies:
  - Junk food consumption was associated with higher rates of depression compared to those with minimal junk food consumption (6 studies, n=48,704; OR 1.2; 95% CI, 1.1–1.2).
  - Junk food consumption was associated with higher rates of stress compared to those with minimal junk food consumption (2 trials, n=100; OR 1.2; 95% CI, 1.1–1.2).

LIMITATIONS:

- The study designs greatly varied.
- The questionnaire tools used to gauge dietary habits had different ways of assessment and were not uniform.
- Some confounding variables were not adequately assessed like seasonal hormonal variations of depressive symptoms.
- Different diagnostic criteria for defining mental health status were used and not uniform.

- The follow-up period was not defined.
- Detailed demographics of participants in the study and control groups were not described.

Sebrina Burnett, DO
University of South Alabama FMRP
Mobile, AL