GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of March 4 - 8, 2024

SPOTLIGHT: CPAP Therapy - Is It Protective Against Recurrent Cardiovascular Events?

- Does Digitally Delivered Physiotherapy Stand Up to Chronic Low Back Pain?
- Early Bird Wins Again in Stroke with AFib
- Does Keto Actually Work?

CPAP Therapy: Is It Protective Against Recurrent Cardiovascular Events?

Adherence to CPAP Treatment and the Risk of Recurrent Cardiovascular Events: A Meta-Analysis

Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, et al. Adherence to CPAP Treatment and the Risk of Recurrent Cardiovascular Events: A Meta-Analysis. *JAMA*. 2023;330(13):1255-1265. doi:10.1001/jama.2023.17465

KEY TAKEAWAY: Adherence to continuous positive airway pressure (CPAP) therapy significantly reduces the risk of recurrent cardiac or cerebrovascular events in patients with moderate to severe obstructive sleep apnea (OSA).

STUDY DESIGN: Systematic review and individual patient data meta-analysis of three randomized controlled trials (N=4,186)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to nonblinded trials)

BRIEF BACKGROUND INFORMATION: OSA is a common condition that leads to an increased risk of cardiac and cerebrovascular events. CPAP therapy is the gold standard treatment of OSA. Previous research has shown that CPAP therapy improves daytime sleepiness and reduces blood pressure, however, the effect of CPAP adherence and risk of recurrent cardiovascular (CV) events is unknown.

PATIENTS: Adults with OSA and known CV disease

INTERVENTION: CPAP treatment

CONTROL: No CPAP treatment

PRIMARY OUTCOME: Major adverse cardiac and cerebrovascular events (MACCEs)

Secondary Outcome: Individual components of the primary composite endpoints including cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, unstable angina, or transient ischemic attack

METHODS (BRIEF DESCRIPTION):

- Participants had preexisting coronary artery disease, cerebrovascular disease, or a history of acute coronary syndrome, and were not considered sleepy, with a mean Epworth Sleepiness Scale score <10 (scale 0–24, with scores of ≥10 indicating concern for OSA).
- The mean age of participants was 60–66 years old, most of whom were male (81–84%) with established OSA from a home sleep test or polysomnography.
- Participants in the intervention group received CPAP treatment in addition to usual care, while participants in the control group received only usual care.
- Individual participant data (IPD) meta-analyses were used in the study according to intention-to-treat principles, and on-treatment analysis was conducted to assess the effect of CPAP adherence.

INTERVENTION (# IN THE GROUP): 2,097

COMPARISON (# IN THE GROUP): 2,089

FOLLOW-UP PERIOD: 39 months

RESULTS:

Primary Outcome –

- There was no difference in MACCEs with CPAP treatment in the intention-to-treat analysis (hazard ratio [HR] 1.0; 95% CI, 0.87–1.2).
- On treatment analysis with CPAP adherence ≥4 hours/day decreased the risk of MACCEs (HR 0.69; 95% CI, 0.52–0.92).

Secondary Outcome –

- In the CPAP group, median adherence was about three hours/day, while 39% of patients had good CPAP adherence (mean ≥4 hours/day).
- None of the individual components mentioned above showed a statistically significant difference between the intervention and control group.

LIMITATIONS:

- The study did not include alternative approaches to OSA treatment other than CPAP.
- There was a low adherence rate to CPAP treatment.
- The included studies were not blinded.
- Participants were predominantly male.
- Most of the patients selected were diagnosed by home sleep apnea tests.
- On-treatment analysis is subject to selection bias.

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Does Digitally Delivered Physiotherapy Stand Up to Chronic Low Back Pain?

Randomized-Controlled Trial Assessing a Digital Care Program versus Conventional Physiotherapy for Chronic Low Back Pain

Cui D, Janela D, Costa F, et al. Randomized-controlled trial assessing a digital care program versus conventional physiotherapy for chronic low back pain. *NPJ Digit Med.* 2023;6(1):121. Published 2023 Jul 7. doi:10.1038/s41746-023-00870-3

KEY TAKEAWAY: Digitally delivered therapy produces similar results to standard in-person physiotherapy in adults with chronic low back pain.

STUDY DESIGN: Single-center, parallel-group, randomized controlled study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic low back pain (CLBP) is not only the world's leading cause of years lived with disability but is also a common primary care complaint that represents a significant economic burden in healthcare costs as well as absenteeism from work. Previous studies have demonstrated the effectiveness of digital exercise-based interventions in the management of CLBP, often improving access and patient adherence to treatment plans. However, only cohort and non-randomized studies have been done to compare asynchronous digital programs to standard in-person physiotherapy.

PATIENTS: Adults with CLBP

INTERVENTION: Digital physiotherapy

CONTROL: Standard care

PRIMARY OUTCOME: Change in disability

Secondary Outcome: Pain, surgery intent, analgesics use, fear-avoidance beliefs (FABs), mental health, physical activity, work productivity impairment (WPAI), patient satisfaction, adherence, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients 18–80 years old who received care at the Emory Orthopedic and Spine Center in Atlanta, Georgia were screened for participation.
- Demographics of study participants:
  - Roughly 40% African American or Black, 25% Caucasian or White, 10% Asian or Pacific Islander, 3% Hispanic or Latino, 1% Native American or Alaskan Native
  - Roughly 70:30 percent ratio of females to males
  - Median BMI of 28 kg/m2
- CLBP was defined as intermittent or persistent low back pain (LBP) for at least 12 weeks and/or ≥50% of the time in the past six months.
- The intervention for the digital group (DG) was eight weeks long and consisted of three 20-minute exercise sessions per week completed asynchronously (independently at their convenience), along with education and cognitive behavior therapy (CBT).
  - Participants in the DG group completed a total of 24 tailored sessions using the tablet provided.
  - Educational reading materials were delivered through a mobile app and a CBT program.
- The control group (CG) attended two 30-minute in-person sessions per week for a total of eight weeks. Sessions included exercise, education, manual therapy (such as joint mobilization and massage), and physical modalities (such as electrical stimulation).
- The primary outcome was a change in disability between baseline and week eight measured using the Oswestry Disability Index (ODI). A score of 0–20% signifies minimal disability while 80–100% indicates that a patient is either bed-bound or experiencing functional impairment.
- Secondary outcomes were measured using a 6-point Likert scale with scores ranging from 0 (none) to 100% (worse). A minimum clinically important difference (MCID) of 10 points or 30% at the eight-week endpoint was used to define a treatment responder.

INTERVENTION (# IN THE GROUP): 70

COMPARISON (# IN THE GROUP): 70

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- Disability in the DG improved compared to baseline (change in ODI score –6.9 points; 95% CI, –19 to –1.6).
- Disability in the CG improved compared to baseline (change in ODI score –6.4 points; 95% CI, –10 to –3.8).

- No differences in pain reduction were seen between the two groups at the eight-week primary endpoint (0.21; 95% CI, −0.76 to 0.84) or overall change (0.30; 95% CI, −0.71 to 1.1) as supported by an effect size of −0.08.

Secondary Outcome –

- There were no differences between DG and CG for pain, mental health, analgesics use, surgery intent, physical activity, patient satisfaction, adherence, FABs, and WPAI.
- The DG group had a lower dropout rate than the CG group (16% vs 34%, respectively; *P*=.019).
- No serious adverse events were reported, and no differences were observed in the rates of adverse events between groups.

LIMITATIONS:

- The intervention was implemented under controlled conditions for a very short period which threatens the external validity of the study.
- The relatively small sample size, lack of blinding, and absence of objective outcome measures are all additional limitations of the study.

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Early Bird Wins Again in Stroke with AFib

Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

Fischer U, Koga M, Strbian D, et al. Early versus Later Anticoagulation for Stroke with Atrial Fibrillation. *N Engl J Med.* 2023;388(26):2411-2421. doi:10.1056/NEJMoa2303048

KEY TAKEAWAY: In patients with an acute ischemic stroke and atrial fibrillation, the risk of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death is lower with early initiation of direct oral anticoagulants (DOACs) compared to late initiation.

STUDY DESIGN: Randomized, double-blind, controlled cohort study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Anticoagulation with DOACs reduces the risk of ischemic stroke and systemic embolism among persons with atrial fibrillation. However, whether the timing of initiating DOAC therapy influences the risks of stroke recurrence and bleeding after an acute ischemic stroke is unclear.

PATIENTS: Adults with atrial fibrillation and acute stroke

INTERVENTION: Early DOAC treatment

CONTROL: Late DOAC treatment

PRIMARY OUTCOME: Composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization

Secondary Outcome: Components of the composite primary outcome at 30 days and 90 days

METHODS (BRIEF DESCRIPTION):

- Patients with a history of acute ischemic stroke and nonvalvular atrial fibrillation were included in the study.
- Participants receiving therapeutic anticoagulation before stroke or during hospitalization for stroke were excluded from the study.
- Participants were randomized 1:1 to either early anticoagulation or later anticoagulation but were stratified using a deterministic minimization method based on age (<70 years old or ≥70 years old) and stroke size.
    - Median age 77 years old.
- Early anticoagulation was defined as within 48 hours for mild or moderate stroke and day six or seven after a major stroke.
- Late anticoagulation was defined as anticoagulation on day three or four after a minor stroke, day six or seven after a moderate stroke, or day 12, 13, or 14 after a major stroke.
- Stroke was defined as abnormal on CT or MRI or clinical symptoms persisted for longer than 24 hours.
- Participants were treated with any direct oral anticoagulants approved for the prevention of stroke or systemic embolism.
- Composite endpoints were determined at 30 days and 90 days.

INTERVENTION (# IN THE GROUP): 1,006

COMPARISON (# IN THE GROUP): 1,007

FOLLOW-UP PERIOD: 30 days and 90 days

RESULTS:

Primary Outcome –

- Early anticoagulation composite events were significantly lower at 30 days than the later-treatment group (number of events 2.9 vs 4.1%, adjusted risk benefit 1.2%; 95% CI, –2.8% to –0.47%).

Secondary Outcome –

- There was no statistical difference between the two groups in any of the individual primary outcome components (recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death) at 30 days or 90 days.

LIMITATIONS:

- Participants were excluded if they were already receiving therapeutic anticoagulation at baseline.
- Participants had a low median NIHSS score.
- The participants were predominately White.

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Does Keto Actually Work?

Effects of 30 Days of Ketogenic Diet on Body Composition, Muscle Strength, Muscle Area, Metabolism, and Performance in Semi-Professional Soccer Players

Antonio Paoli A, Mancin L, Caprio M, et al. Effects of 30 days of ketogenic diet on body composition, muscle strength, muscle area, metabolism, and performance in semi-professional soccer players. *J Int Soc Sports Nutr.* 2021;18(1):62. Published 2021 Sep 16. doi:10.1186/s12970-021-00459-9

KEY TAKEAWAY: Short-term ketogenic diets may be effective for body fat loss while maintaining muscle mass and athletic performance in semi-professional soccer athletes.

STUDY DESIGN: Randomized control trial

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

BRIEF BACKGROUND INFORMATION: Ketogenic is widely touted as a fat loss fad diet and is often misused as a method of fat loss. In theory and when used properly, ketogenesis can be an effective way to lose body fat while maintaining muscle mass. This study demonstrates an effective way to use a ketogenic diet for fast and controlled weight loss while still maintaining musculature and athletic performance.

PATIENTS: Soccer athletes

INTERVENTION: Ketogenic diet (KD)

CONTROL: Western diet (WD)

PRIMARY OUTCOME: Body composition, muscle strength, muscle area, metabolism, and performance

METHODS (BRIEF DESCRIPTION):

- Subjects consisted of 16 semi-professional Italian soccer players from the same team.
- Subjects were randomly assigned to a ketogenic diet and a Western diet.
- Subjects received nutrition counseling, a meal plan, food diaries, and were encouraged to drink plenty of water.
- Body weight, body composition, resting energy expenditure, muscle cross-sectional area, muscle strength as well as the yo-yo intermittent recovery test time were measured.
- Results measured body fat, visceral adipose tissue, waist circumference, and extra-cellular water comparatively between the two groups.
- Lean soft tissue of the quadriceps muscle area and maximal strength were also measured.

INTERVENTION (# IN THE GROUP): 8

COMPARISON (# IN THE GROUP): 8

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Compared to the WD, the KD reduced:
  - Fat Mass (KD –7.9 vs WD –4.9, *p*=.036)
  - Visceral adipose tissue (KD –16 vs WD –8.0, *p*=.0018)
  - Waist circumference (KD –4.7 vs WD –1.5, *p*=.019)
  - Extra-cellular water (KD –3.6 vs WD 0.05, *p*=.006)
  - Respiratory exchange ratio (KD –14 vs WD –2.9, *p*=.0008)
- Yo-yo intermittent test improved significantly in both groups without significant differences between groups (KD 28 vs WD 45, *P*<.0001).
- The countermovement jump significantly improved in the KD group (8.5, *p*=.0021).
- Lean soft tissue, quadriceps muscle area, maximal strength, and resting energy expenditure showed no changes in both groups.

LIMITATIONS:

- The sample size was small.
- Subjects were accustomed to rigorous training schedules and high levels of physical activity.
- The study is not generalizable to the lay population.

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