GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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One Step at a Time: A Shift in First-Line Therapy for Patients with Peripheral Artery Disease

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Home-Based Walking Exercise and Supervised Treadmill Exercise in Patients with Peripheral Artery Disease: An Individual Participant Data Meta-Analysis

Thangada ND, Zhang D, Tian L, et al. Home-Based Walking Exercise and Supervised Treadmill Exercise in Patients With Peripheral Artery Disease: An Individual Participant Data Meta-Analysis. *JAMA Netw Open.* 2023;6(9):e2334590. Published 2023 Sep 5. doi:10.1001/jamanetworkopen.2023.34590

KEY TAKEAWAY: Home-based walking exercise significantly increases the six-minute walk distance (6MW) compared to supervised treadmill exercise, currently considered first-line therapy for peripheral artery disease (PAD).

STUDY DESIGN: Meta-analysis of five randomized controlled trials (N=719)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Despite being the first-line treatment for PAD, many people do not participate in supervised treadmill exercise. Home-based walking exercise is more convenient. Only one clinical trial with patients with PAD has compared the effects of supervised treadmill exercise with home-based walking exercise on 6MW.

PATIENTS: Adults with PAD

INTERVENTION: Home-based walking exercise

CONTROL: Supervised treadmill exercise

PRIMARY OUTCOME: 6MW distance, maximum treadmill walking distance, walking speed

METHODS (BRIEF DESCRIPTION):

- Participants in the studies were adults with PAD with one of the following:
  - Ankle Brachial Index (ABI) of ≤0.90 in four of the trials and an ABI of ≤0.95 in one of the trials
  - ABI >0.90 but with radiographic or vascular testing showing lower extremity atherosclerosis with 70% stenosis or more
  - ABI 0.91–1.0 at baseline whose ABI dropped by 20% or more after a heel-rise test
- Exclusion criteria included:
  - Chronic limb-threatening ischemia, foot ulcers, significant visual or hearing impairment, walking impairment not due to PAD, above or below-the-knee amputations, and patients who are wheelchair-bound.
  - Recent major surgery or revascularization, and people who had participated in cardiac rehabilitation or supervised exercise program within the past three months.
  - People with abnormal exercise stress tests at baseline unless follow-up cardiac testing revealed no significant coronary heart disease.
- Supervised treadmill exercise interventions comprised of three exercise sessions per week with an exercise physiologist. Patients were asked to walk at a pace to induce ischemic leg symptoms for 10–15 min in week one and then work up to 50 min of exercise per session if possible.
- Home-based walking interventions comprised of patients walking near or around the home, five days/week beginning at 15–20 min per day and working up to 50 min; these interventions did include coach feedback.
- In the 6MW test, 8 m represented a small clinically important difference and 20 m represented a large clinically important difference.
- The Walking Impairment Questionnaire (WIQ) is a specific questionnaire that measures patient-reported difficulty in three domains (distance, walking speed, and stair-climbing) using a 0–100 scale (100=best).
- Analysis of covariance and individual participant data meta-analysis was performed for each study to evaluate between-group differences.
- Individual participant data was analyzed using analysis of covariance adjusting for age, sex, race, baseline value for each outcome, study, and baseline variables that differed significantly with p <0.05 (cigarette smoking, history of MI, heart failure).

INTERVENTION (# IN THE GROUP): 349

COMPARISON (# IN THE GROUP): 370

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Home-based walking exercise improved 6MW distances more than supervised treadmill exercise

(adjusted between-group difference 24; 95% CI, 3.6–44).

- Home-based walking exercise resulted in significantly less improvement in maximum treadmill walking distance compared to supervised treadmill exercise (difference 133 m; 95% CI, 72–193).
- Home-based walking exercise improved mean walking speed compared to supervised treadmill exercise (difference 7.0; 95% CI, 0.3–14).

LIMITATIONS:

- The home-based walking exercise tested highly effective interventions with coaching feedback and weekly monitoring which may limit generalizability.
- The data obtained from the randomized clinical trials were led by one investigative team.
- The data integrated from the randomized clinical trials and comparisons were not determined in advance thus increasing possible bias.

Judith Philip, MD
IUSM Arnett FMRP
Lafayette, IN

Mindfulness for Headaches and Chronic Migraines

Efficacy of Mindfulness Added to Treatment as Usual in Patients with Chronic Migraine and Medication Overuse Headache: A Phase III Single-Blind Randomized-Controlled Trial (The MIND-CM Study)

Grazzi L, D'Amico D, Guastafierro E, et al. Efficacy of mindfulness added to treatment as usual in patients with chronic migraine and medication overuse headache: A phase-III single-blind randomized-controlled trial (the MIND-CM study). *J Headache Pain.* 2023;24(1):86. Published 2023 Jul 14. doi:10.1186/s10194-023-01630-0

KEY TAKEAWAY: Mindfulness in addition to a treat as usual (TaU) approach is superior to TaU alone in reducing headache frequency and medication use while improving quality of life (QoL).

STUDY DESIGN: Phase-III single-blind randomized-controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic migraine (CM) and medication overuse headache (MOH) patients have a high disease burden of ≥15 monthly headache days, and relief medication overuse over three months. This is commonly treated by supervised medication withdrawal, patient education, and prophylaxis initiation. Primary care physicians are well-positioned to diagnose, treat, and integrate mindfulness into their practice. Few RCTs on mindfulness for headaches exist. This study aimed to address alternatives/adjuncts to standard CM and MOH treatment protocols.

PATIENTS: Patients with CM and MOH

INTERVENTION: TaU + mindfulness

CONTROL: TaU

PRIMARY OUTCOME: Headache frequency reduction
Secondary Outcome: QoL, disability, work-related activities impact, loss of productive time (LPT), disease cost, headache impact, depression, anxiety, cutaneous allodynia, self-awareness, medication intake

METHODS (BRIEF DESCRIPTION):

- 177 adults (89% females and 11% males), with a median age of 48 years old, treated at an Italian headache center, with no prior mindfulness experience were included in the study.
- Unblinded patients were randomized 1:1 into the following groups:
  - TaU: Medication overuse supervised withdrawal, followed by education and initiation of prophylaxis (i.e antihypertensives, antiepileptics, antidepressants).
  - TaU + mindfulness: TaU plus six weeks of weekly, 90-minute mindfulness training sessions, emphasizing symptom insight and acceptance to help recognize the need for medications and reduce overuse. A home meditation audio was provided for 7, 10-minute practice sessions.
- Two neurologists conducted the study. One blinded neurologist enrolled and followed patients, while the other led mindfulness sessions.
  - Unblinded researchers handled randomization and data collection.
- Data was taken at baseline and follow-up visits at three, six, and 12 months from enrollment into the study.
- Primary outcome was measured using structured headache diaries with a goal of >50% reduction in headache frequency at 12 months compared to baseline.
- Secondary outcomes were measured using:
  - Headache impact was assessed using the six-item headache impact test (HIT-6).
    - Scores range from 26–78, with higher scores indicating a greater headache impact.
    - A score change ≥6 represented a clinically meaningful improvement.
  - Quality of life was assessed using the 14-item Migraine-Specific Quality of Life Questionnaire 2.1 (MSQ v2.1).
    - Scaled scores range from 0–100 with higher scores indicating a better quality of life.
  - Disability was assessed using the seven-item Migraine Disability Assessment (MIDAS) and the 12-item WHO Disability Assessment Schedule (WHODAS-12).
    - MIDAS scores range from 0–270, with higher scores indicating greater disability.

        - WHODAS-12 scores range from 0–100, with higher scores indicating greater disability.
    - Work-related activities impact was calculated by the 17-item two-scale HEADWORK questionnaire and a daily equivalent LPT.
        - HEADWORK scores are scaled 0–100, with higher scores indicating a higher impact on work-related activity.
        - LPT was measured in day-equivalents (absenteeism vs presenteeism) with an estimation of their performance on a 1–99% scale.
    - Depression and anxiety were assessed by the 21-item Beck Depression Inventory-II (BDI-II) and the 40-item State-Trait Anxiety Inventory (STAI-Y).
        - BDI-II scores range from 0–63, with higher scores indicating a higher severity of depression.
        - STAI-Y scores range from 20–80, with higher scores indicating higher severity of anxiety.
    - Cutaneous allodynia is assessed by a 12-item Allodynia Symptoms Checklist (ASC-12).
        - Scores range from 0–24, with higher scores indicating an increased severity of allodynia.
    - Self-awareness was assessed using the 15-item Mindful Attention and Awareness Scale (MAAS).
        - Scores range from 15–90, with higher scores indicating greater mindfulness.
    - Medication use was measured as intake of NSAIDS, triptans, and total drug intake.
    - Disease costs included total, direct, indirect, and non-healthcare costs.

INTERVENTION (# IN THE GROUP): 88

COMPARISON (# IN THE GROUP): 89

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Patients in the TaU + mindfulness group had greater headache frequency reduction over 12 months compared to patients in the TaU group (78% vs 48%, respectively; $p<.0001$, chi-squared 17).

Secondary Outcome –

- TaU + mindfulness improved the following compared to TaU:
    - QoL (results presented via figure)
    - Disability (results presented via figure)
    - Headache impact (odds ratio [OR] 2.5; 95% CI, 1.3–4.7)
    - Costs (except for direct non-healthcare costs, results presented via figure)
        - Total costs (results presented via figure, $p<.0001$)
        - Indirect costs (results presented via figure, $p=.0004$)
        - Direct healthcare costs (results presented via figure, $p=.007$)
    - LPT (results presented via figure, $p=.0086$)
    - NSAID use (results presented via figure, $p<.0001$)
    - Total drug intake (results presented via figure, $p=.0001$)
- There was no difference between TaU + mindfulness and TaU in scales for depression, anxiety, cutaneous allodynia, self-awareness, work-related activities, and one disability scale.

LIMITATIONS:

- Generalizability is limited given that this is a single-center study of mostly female patients.
- The COVID-19 pandemic interrupted the trial, restricting access to care.
- Mindfulness adherence was measured but not reported.
- The TaU group lacked standardization in medication choice and patient education.
- Adverse events during mindfulness practice were not recorded as it was assumed to be free of side effects.

Shany Freund Maravankin, MD
Northeast Georgia Medical Center
Gainesville, GA

Does Solanezumab Slow the Onset of Alzheimer's Disease?

Trial of Solanezumab in Preclinical Alzheimer's Disease
Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. *N Engl J Med. 2023*;389(12):1096-1107. doi:10.1056/NEJMoa2305032

KEY TAKEAWAY: Solanezumab does not change the progression of cognitive decline in patients with elevated amyloid beta deposits in the brain after 4.5 years of treatment.

STUDY DESIGN: Multicenter, double-blind, randomized, placebo-controlled study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Elevated amyloid-beta deposits in the brain are associated with dementia. Higher levels of amyloid-beta deposits may pose an increased risk of new-onset dementia. Previous studies have shown that solanezumab reduces amyloid-beta deposition in the brain. This study aimed to determine if solanezumab treatment could reduce the risk of new-onset dementia.

PATIENTS: Individuals with elevated amyloid deposition in the brain

INTERVENTION: Solanezumab

CONTROL: Placebo

PRIMARY OUTCOME: Change in cognition

METHODS (BRIEF DESCRIPTION):

- Participation was limited to those 65–85 years old living independently without cognitive impairment, with elevated amyloid-beta deposits in the brain quantified by positron emission tomography (PET) scan.
- Participants were randomized 1:1 ratio to receive either solanezumab or a placebo.
- Participants in the treatment group were initially administered intravenous (IV) solanezumab 400 mg every four weeks.
- Treatment was modified to 1600 mg IV solanezumab every four weeks in 2017 due to results of a phase three trial suggesting 400 mg dose may be inadequate.
    - The trial length was extended to accommodate the dose change.
- The placebo group was matched and assigned randomly.
- Baseline cognitive status was assessed with the Clinical Dementia Rating (CDR) score, a 3-point rating (0–3) system where zero indicates no cognitive impairment and three indicates severe dementia.
- Change in the cognition of trial participants during the trial was measured using the Preclinical Alzheimer Cognitive Composite (PACC) score. PACC is a 96-point rating (range of 0-96) system where lower scores indicate increasing memory impairment.

INTERVENTION (# IN THE GROUP): 578

COMPARISON (# IN THE GROUP): 591

FOLLOW-UP PERIOD: 4.5 years

RESULTS:

Primary Outcome –

- There was no statistically significant difference change in cognition with solanezumab compared to placebo (between-group difference −0.30; 95% CI, −0.82 to 0.22).
    - Solanezumad (mean change −1.4; 95% CI, −1.8 to −1.0)
    - Placebo (mean change −1.1; 95% CI, −1.5 to −0.81)

LIMITATIONS:

- The trial length was not long enough to see a cognitive decline in participants after 4.5 years.
- The number of African American participants was limited, limiting generalized conclusions.
- Solanezumab dose changed mid-trial due to new information suggesting the trial dose was not therapeutic.
- The COVID-19 pandemic disrupted trial activities.

Robert Grove, DO
Community Health Care FMRP
Tacoma, WA

Cannabis and Pregnancy: Unraveling Adverse Outcomes via Placental Function

Cannabis Exposure and Adverse Pregnancy Outcomes Related to Placental Function

Metz TD, Allshouse AA, McMillin GA, et al. Cannabis Exposure and Adverse Pregnancy Outcomes Related to Placental Function. *JAMA*. 2023;330(22):2191-2199. doi:10.1001/jama.2023.21146

KEY TAKEAWAY: Cannabis exposure during pregnancy is associated with adverse outcomes related to placental function.

STUDY DESIGN: Prospective multicenter cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Rising maternal cannabis usage, fueled by increased accessibility and perceived safety, presents a significant concern. Previous studies faced challenges, including underreported use and confounding factors like concurrent alcohol and nicotine intake. A comprehensive evaluation with biological sampling is essential to understand the impact of cannabis on pregnancy outcomes.

PATIENTS: Nulliparous individuals

INTERVENTION: Cannabis exposure during pregnancy

CONTROL: No cannabis exposure during pregnancy

PRIMARY OUTCOME: Composite outcome of small-for-gestational-age, medically indicated preterm birth, stillborn, or hypertensive disorders of pregnancy

Secondary Outcome: Individual primary outcomes, cesarean birth, spontaneous preterm birth, placental abruption, NICU admission, neonatal morbidity, neonatal death

METHODS (BRIEF DESCRIPTION):

- This was an ancillary analysis of nulliparous patients treated at eight US medical centers.
- Drug assays and analyses were completed from June 2020–April 2023.
- Urine immunoassay for 11-nor-carboxy Δ 9-tetrahydrocannabinol from frozen samples from first to third-trimester pregnancy was used to ascertain cannabis exposure.
- Positive findings were validated with liquid chromatography-tandem spectrometry.
- For the primary outcome analysis, cannabis exposure during part of the pregnancy was categorized dichotomously (present or absent).
- A secondary analysis of the primary outcome compared the timing of cannabis exposure as first trimester only or ongoing exposure throughout pregnancy.
- A planned secondary exploratory analysis defined cannabis exposure as the observed quantitative THC-COOH levels in the first trimester and subsequent average cumulative cannabis exposure during the pregnancy calculated from visits one, two, and three.

INTERVENTION (# IN THE GROUP): 610

COMPARISON (# IN THE GROUP): 8,647

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- Cannabis use during pregnancy was associated with an increased risk for the primary composite outcome (adjusted relative risk [aRR] 1.3; 95% CI, 1.1–1.5).

Secondary Outcome –

- Cannabis exposure during any stage of pregnancy was associated with an increased likelihood of delivering small-for-gestational-age (aRR 1.5; 95% CI, 1.1–2.1).
- There were no significant group differences in cesarean birth, spontaneous preterm birth, placental abruption, NICU admission, neonatal morbidity, or neonatal death.
- Cannabis use during the first trimester only was not associated with the primary composite outcome.
- Ongoing cannabis use during pregnancy was associated with the primary composite outcome (aRR 1.3; 95% CI, 1.1–1.6).

LIMITATIONS:

- Degradation of THC-COOH metabolites in older urine samples.
- The mode of cannabis exposure was unclear.
- Modern cannabis products have higher THC concentrations and may not correlate to concentrations used during the study period.
- Urine assays used for ethanol may underestimate alcohol use given its low sensitivity and ability to detect alcohol when used within a few hours before specimen collection.

- Observational studies can only determine associations and not causality.

Kuvera Sikhakhane, MD
IUSM Arnett FMRP
Lafayette, IN