GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 17-21, 2025

SPOTLIGHT:

More Medicine, More Problems

- Honest Conversations: Maternal Dangers of Cannabis Use in the Prenatal Period
- The Impact of Fish Oil Supplements on the Progression of Cardiovascular Diseases
- Head or Heart: The Cardiovascular Risks of Long-Term ADHD Medication Use
- Goodnight: A New Frontier in Managing Insomnia Among Breast Cancer Survivors with Smart Speakers

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Medication Optimization Protocol Efficacy for Geriatric Inpatients: A Randomized Clinical Trial

Ie K, Hirose M, Sakai T, et al. Medication Optimization Protocol Efficacy for Geriatric Inpatients: A Randomized Clinical Trial [published correction appears in JAMA Netw Open. 2024 Nov 4;7(11):e2449465. doi: 10.1001/jamanetworkopen.2024.49465.]. *JAMA Netw Open*. 2024;7(7):e2423544. Published 2024 Jul 1. doi:10.1001/jamanetworkopen.2024.23544

KEY TAKEAWAY: For older inpatient adults, deprescribing interventions help reduce unnecessary medications, but they do not significantly impact rates of death, hospital visits, or rehospitalization within 12 months.

STUDY DESIGN: Single-center, non-blinded randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Polypharmacy is the prescription of multiple medications, and it is a significant and rising medical concern in the growing elderly population. This is a source of significant morbidity and mortality and contributes to ballooned health care expenses. This study aimed to investigate the effect of a team-based medication optimization program on patient survival, and unscheduled inpatient admissions and readmissions among older patients meeting criteria for polypharmacy.

PATIENTS: Inpatient adults ≥65 years old receiving ≥5 regular medications

INTERVENTION: Medical optimization

CONTROL: Usual care

PRIMARY OUTCOME: Composite of all-cause death, unscheduled hospital visits, and rehospitalization
Secondary Outcome: Prescribed medications, level of long-term care required, health-related quality of life, adverse events, all-cause death

METHODS (BRIEF DESCRIPTION):

- Included patients were adults admitted to the community hospital, with the ability to take oral medication, whose hospital stay was expected to be ≥1 week.
- Participants divided by age group and randomly allocated within strata to intervention and usual care groups by block randomization.
- The intervention consisted of baseline data collection, and medication review, followed by a medication optimization proposal consisting of assessment of medication indication, balancing benefits & harms, evaluating symptom provoking medications, and evaluation of preventative medications.
    - Medication review was completed using the STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert to Right Treatment) criteria.
- Usual care consisted of pharmacist-reviewed medication reconciliation.
- The patient's medication plan was relayed to the provider (PCP) and the community pharmacist upon discharge.
- Primary outcome was a composite of all cause death, unscheduled hospital visits, and rehospitalization within 48 weeks of enrollment.
- Secondary outcomes include number of regular medications and potentially inappropriate medications (PIM) based on STOPP/START criteria, level of long-term care required, health-related quality of life, adverse events, falls, and all cause death during initial hospitalization.
    - The health-related quality of life was measured using the EuroQol 5 Dimensions 3-Level. Scores range from 0–1, with higher scores indicating a better health-related quality of life.

INTERVENTION (# IN THE GROUP): 215

COMPARISON (# IN THE GROUP): 227

FOLLOW-UP PERIOD: Six and 12 months

RESULTS:

Primary Outcome –

- There was no significant difference in composite all-cause death, unscheduled hospital visits, and rehospitalization within 12 months for participants receiving medical optimization compared to usual care (stratified hazard ratio [HR] 0.98; 95% CI, 0.75–1.3).

Secondary Outcome –

- Medical optimization resulted in fewer prescribed medications compared to usual care at six and 12 months.

    - Six months (mean difference [MD] 0.92; 95% CI, 0.37–1.5)
    - 12 months (MD 0.62; 95% CI, 0.03–1.2)
- Medical optimization resulted in lower percentage of patients with ≥1 PIMs compared to usual care at six and 12 months.
    - Six months (adjusted odds ratio [aOR] 0.50; 95% CI, 0.29–0.86)
    - 12 months (aOR 0.45; 95% CI, 0.25–0.80)
- There was no significant difference for the level of long-term care required, health-related quality of life, adverse events, falls, and all-cause death during initial hospitalization for participants receiving medical optimization compared to usual care.

LIMITATIONS:

- The lack of blinding for both participants and the team responsible for the deprescribing intervention may have introduced bias into the study.
- The study setting may have influenced physicians' medication decisions, potentially limiting the generalizability of the results.
- The study was conducted on patients in an inpatient setting with admission stays of ≥1, which also may limit the applicability of the findings to general clinic practice.

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Honest Conversations: Maternal Dangers of Cannabis Use in the Prenatal Period

Prenatal Cannabis Use and Maternal Pregnancy Outcomes

Young-Wolff KC, Adams SR, Alexeeff SE, et al. Prenatal Cannabis Use and Maternal Pregnancy Outcomes. *JAMA Intern Med.* 2024;184(9):1083-1093. doi:10.1001/jamainternmed.2024.3270

KEY TAKEAWAY: Prenatal cannabis use increases risk of gestational hypertension, preeclampsia, and inadequate or excessive weight gain, but decreases risk of gestational diabetes.

STUDY DESIGN: Retrospective population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Little is known about how prenatal cannabis use affects fetal and neonatal outcomes, and even less has been studied about its effects on maternal health outcomes in pregnancy. This retrospective cohort study examined the association of prenatal cannabis use with maternal development of pregnancy-related conditions and assessed whether risk changes with frequency of use.

PATIENTS: Pregnant persons

INTERVENTION: Cannabis use

CONTROL: No cannabis use

PRIMARY OUTCOME: Maternal complications of pregnancy

Secondary Outcomes: Dose-dependent risk of gestational diabetes and gestational hypertension

METHODS (BRIEF DESCRIPTION):

- This study was conducted within the Kaiser Permanente Northern California (KPNC) Healthcare System, which included singleton pregnancies from 2011–2019 that reached ≥20 weeks estimated gestational age (EGA) and that had ≥1 prenatal visits.
- Patients who did not respond to the self-reported cannabis use question or who did not have a THC urine toxicology test were excluded.
- Primary exposure was determined by universal screening at 8–10 weeks EGA via a self-administered questionnaire and urine drug screen (confirmed with testing for a cannabis metabolite via liquid chromatography).
- Self-reported frequency of prenatal cannabis use was assigned to mutually exclusive categories of daily, weekly, monthly or less, never, or unknown.
- The primary outcome assessed the development of gestational hypertension, preeclampsia, or gestational diabetes, and weight gain above or below recommendations.
- The secondary outcomes assessed the dose-dependent risk of gestational diabetes and gestational hypertension.
- Outcomes were determined using a combination of vital signs, medication usage, inpatient and outpatient diagnosis codes, and registration to the KPNC Gestational Diabetes Registry.
- Covariates included maternal age at pregnancy onset, race/ethnicity, parity, maternal insurance, pre-pregnancy body mass index (BMI), neighborhood deprivation index, and comorbidities (pregestational diabetes, psychiatric disorders, non-cannabis substance use, nausea, and vomiting).
- Statistical analysis included unadjusted risk ratios and adjusted risk ratios with 95% confidence intervals.

INTERVENTION (# IN THE GROUP): 20,053

COMPARISON (# IN THE GROUP): 269,669

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Prenatal cannabis use was associated with an increased risk of the following compared to no cannabis use:
  - Gestational hypertension (adjusted risk ratio [aRR] 1.2; 95% CI, 1.1– 1.2)
  - Preeclampsia (aRR 1.1; 95% CI, 1.01–1.2)
  - Gestational weight gain less than guidelines (aRR 1.1; 95% CI, 1.01–1.1)
  - Gestational weight gain greater than guidelines (aRR 1.1; 95% CI, 1.1–1.1)
- Prenatal cannabis use was associated with a decreased risk of gestational diabetes compared to no cannabis use (aRR 0.89; 95% CI, 0.85–0.94).
- Prenatal cannabis use was not significantly associated with eclampsia, placenta accreta, placenta previa, or severe maternal morbidity in the

fully adjusted models, although these outcomes were very rare.

Secondary Outcome –

- There was a dose-response association between frequency of use of cannabis and risk of development of gestational hypertension:
  - Daily cannabis use was associated with the highest risk of development of gestational hypertension (aRR 1.2; 95% CI, 1.1–1.4).
  - Weekly cannabis use was associated with a moderately increased risk of developing gestational hypertension (aRR 1.2; 95% CI, 1.1–1.3).
  - Monthly or less cannabis use was not associated with an increased risk of developing gestational hypertension.
  - An unknown frequency of cannabis use was associated with an increased risk of developing gestational hypertension (aRR 1.2; 95% CI, 1.2–1.3).
- There was a decreased risk of developing gestational diabetes with monthly or less cannabis use (aRR 0.89; 95% CI, 0.79–0.98) and with unknown frequency of cannabis use (aRR 0.89; 95% CI, 0.83–0.95).

LIMITATIONS:

- The study excluded uninsured patients, limiting generalizability.
- There may have been confounders not measured by the authors.
- The results of the study were collected in a state where medicinal cannabis has been legal since 1996, and legal adult sales since 2018.
- Urine tests for prenatal cannabis use could have detected pre-pregnancy use in some adults and may be more likely to detect heavy use.
- Specific cannabis products, potency, and modes of administration (smoking vs edibles) were not assessed.

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The Impact of Fish Oil Supplements on the Progression of Cardiovascular Diseases

Regular Use of Fish Oil Supplements and Course of Cardiovascular Diseases: Prospective Cohort Study

Chen G, Qian ZM, Zhang J, et al. Regular use of fish oil supplements and course of cardiovascular diseases: prospective cohort study. *BMJ Med*. 2024;3(1):e000451. Published 2024 May 21. doi:10.1136/bmjmed-2022-000451

KEY TAKEAWAY: Regular use of fish oil supplements may increase the risk of atrial fibrillation (AF) but slightly decrease the risk of death in individuals without cardiovascular disease (CVD), and reduces the risk of AF transitioning to major adverse cardiovascular events (MACE).

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: CVD is the leading cause of death worldwide. Omega-3 fatty acids in fish oil are recommended for cardiovascular health, but their benefits and risks are debated. This study aimed to evaluate the effects of regular fish oil supplementation on the progression of CVD, assessing its role at different stages of disease development and progression.

PATIENTS: Adults without CVD

INTERVENTION: Fish oil supplements

CONTROL: No fish oil supplements

PRIMARY OUTCOME: AF, MACE, death

Secondary Outcome: Disease progression

METHODS (BRIEF DESCRIPTION):

- The study included 415,737 adults 40–69 years old without pre-existing cardiovascular disease, enrolled in the UK Biobank study, 31% of whom took fish oil supplements regularly at baseline.
- Participant age, sex, ethnic group, urban or rural setting, body mass index (BMI), socioeconomic status (Townsend deprivation index), and dietary habits including consumption of oily fish, non-oily fish, vegetables, fruit, and red meat were collected at baseline.
- Participants' smoking status, alcohol consumption, and physical activity were also collected at baseline.
- Participants were followed from 2006–2021.
- Patients with prior AF, heart failure (HR), myocardial infarction (MI), stroke, or cancer were excluded from the study.
- Participants were classified as regular users or non-users of fish oil supplements based on self-reported data collected during a baseline survey.
    - Dosages, frequencies, and formulations of fish oil supplements were not specified.
- Incidence of atrial fibrillation, MACE, and death were identified through linkage to hospital records and death registries.
    - MACE encompassed HF, stroke, and MI.
- Multi-state regression models were used to assess the association of fish oil use with transitions between disease states, including progression from a healthy state to AF, from AF to MACE, AF to HF, AF to MI, and AF to stroke.

INTERVENTION (# IN THE GROUP): 130,365

COMPARISON (# IN THE GROUP): 285,372

FOLLOW-UP PERIOD: Mean 12 years

RESULTS:

Primary Outcome –

- Regular use of fish oil supplements was associated with an increased risk of AF compared to no use in healthy individuals (n=18,367; hazard ratio [HR] 1.1; 95% CI, 1.1–1.2).
- Regular use of fish oil supplements was not associated with an increased risk of MACE compared to no use in healthy individuals (n=17,826; HR 1.0; 95% CI, 0.97–1.0).
- Regular use of fish oil supplements does not increase the risk of death compared to no use in healthy individuals (n=14,902; HR 0.98; 95% CI, 0.95–1.0).

Secondary Outcome –

- Regular use of fish oil supplements was associated with a decreased risk of transitioning from AF to MACE compared to no use (n=4,810; HR 0.92; 95% CI, 0.87–0.98).
- Regular use of fish oil supplements was associated with a decreased risk of transitioning from AF to MI compared to no use (n=1,415; HR 0.85; 95% CI, 0.76–0.96).

- Regular use of fish oil supplements did not demonstrate a protective effect compared to no use in transitioning from AF to HF (n=3,085; HR 0.95; 95% CI, 0.88–1.0).
- Regular use of fish oil supplements did not demonstrate a protective effect compared to no use in transitioning from AF to stroke (n=1,180; HR 1.0; 95% CI, 0.89–1.1).

LIMITATIONS:

- The cohort design limited causal inference, allowing the potential for unmeasured confounders.
- Recall bias of participants' self-reported fish oil use
- The predominantly White cohort (95% of participants) restricted applicability to diverse groups.
- Clinical applicability was hampered since dosage, frequency, and formulation of fish oil supplements were not specified, and changes in supplement use during follow-up were not assessed.
- AF incidence may have been underestimated since less severe cases may not have presented to the hospital.

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Head or Heart: The Cardiovascular Risks of Long-Term ADHD Medication Use

Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases

Zhang L, Li L, Andell P, et al. Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases. *JAMA Psychiatry*. 2024;81(2):178-187. doi:10.1001/jamapsychiatry.2023.4294

KEY TAKEAWAY: Patients with attention deficit/hyperactivity disorder (ADHD) who are prescribed a stimulant ≥5 years are more likely to develop cardiovascular disease (CVD). This should be discussed as part of shared medical decision making for ADHD management.

STUDY DESIGN: Nested case-control study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: ADHD medications are effective but have been associated with elevated heart rate and blood pressure in the short term. There is little research about their long-term cumulative effects. Many primary care patients with ADHD continue the medication for decades, which could be affecting their long-term CVD outcomes.

PATIENTS: Patients with diagnosed ADHD

INTERVENTION: ADHD patients who developed CVD

CONTROL: ADHD patients without CVD

PRIMARY OUTCOME: Association of duration of ADHD pharmacotherapy and development of CVD

METHODS (BRIEF DESCRIPTION):

- Swedish patients 6–64 years old with a diagnosis of ADHD or dispensation of ADHD medications (methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, atomoxetine, and guanfacine) were identified using Swedish national databases.
- Patients on ADHD medications who developed CVD after ≥3 months into the study were indexed as cases and compared to up to five matched controls.
- Crude odds ratios (ORs) were calculated for associations between the total duration of ADHD medication and CVD.
- Adjusted ORs (aORs) were then calculated and controlled for age, sex, calendar time, average defined daily dose (DDD) of medication, and comorbid medical conditions such as obesity, type 2 diabetes (T2DM), and hyperlipidemia (HLD).

INTERVENTION (# IN THE GROUP): 10,388

COMPARISON (# IN THE GROUP): 51,672

FOLLOW-UP PERIOD: January 1, 2007–December 31, 2020

RESULTS:

Primary Outcome –

- Patients using ADHD medication for 3–5 years were more likely to develop CVD than patients not on ADHD medication (aOR 1.3; 95% CI, 1.2–1.4).
- Patients using ADHD medication for >5 years were more likely to develop CVD than patients not on ADHD medication (aOR 1.2; 95% CI, 1.1–1.4).
- Patients using atomoxetine only for the first year of use were more likely to develop CVD than patients not on atomoxetine (aOR 1.2; 95% CI, 1.01–1.1).
- Incident CVD was similar in both males and females taking ADHD medications.
- Incidence of CVD was similar between those <25 years old and those >25 years old.

LIMITATIONS:

- All individuals in this study were Swedish, so the results may not be generalizable to other racial or ethnic groups.
- The included patients may not have taken the medication as prescribed.
- Other psychotropic medications may have further increased risk of CVD in those taking ADHD medications.
- Patients may have been misclassified in the searched health registries.
- A case-control study cannot prove causality.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the US Government.

Goodnight: A New Frontier in Managing Insomnia Among Breast Cancer Survivors with Smart Speakers

Voice-Activated Cognitive Behavioral Therapy for Insomnia: A Randomized Clinical Trial

Starling CM, Greenberg D, Lewin D, et al. Voice-Activated Cognitive Behavioral Therapy for Insomnia: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(9):e2435011. Published 2024 Sep 3. doi:10.1001/jamanetworkopen.2024.35011

KEY TAKEAWAY: A smart speaker-based program improves insomnia symptoms compared to web-based educational content in breast cancer survivors.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: Digital cognitive behavioral therapy for insomnia (CBT-I) interventions delivered online have proven effective, improving access to treatment. Recent research has also explored voice-activated programs for managing chronic conditions and supporting cancer patients during chemotherapy, creating new opportunities for home-based engagement. However, this technology has not yet been used for CBT-I. Smart speakers could enhance CBT-I accessibility by mimicking therapist interactions through voice.

PATIENTS: Breast cancer survivors

INTERVENTION: CBT-I smart speaker program

CONTROL: Web-based educational content

PRIMARY OUTCOME: Insomnia symptoms

Secondary Outcome: Change in sleep-related domains

METHODS (BRIEF DESCRIPTION):

- The study team screened participants by phone from Love Research Army of the Dr. Susan Love Foundation, local survivorship groups, and an urban breast medical oncology clinic.
- Inclusion was focused on women, particularly those who were Black or African American, ≥18 years old, who were breast cancer survivors and had not received other behavioral sleep treatments in the past year and attended survivorship visits.
- At baseline, participants completed the Insomnia Severity Index (ISI) and the Consensus Sleep Diary (CSD) for 10 consecutive days.
- Scores on the ISI range from 0–28 points. A score of 0–7 indicates not clinically significant insomnia, a score of 8–14 indicates subthreshold insomnia, a score of 15–21 indicates moderately severe clinical insomnia, and a score of 22–28 indicates severe clinical insomnia.
- If participants scored >7 on ISI, they were included in the study.
- If participants completed at least seven CSDs during the run-in period, they were randomized into the study.
- Participants were randomized 1:1 into either CBT-I smart speaker intervention or web-based educational support.
- Participants in the intervention group received an Echo Dot (third generation) smart speaker with a voice-activated program called "Faster Asleep."
    - For six weeks, the program offered education on CBT-I components, including sleep restriction, schedule modifications, stimulus control, and sleep hygiene, based on data collected through sleep diaries.
    - Recommendations were tailored to participants based on their responses to intake data and daily sleep diary responses.
- Participants in the control group were given access to a website developed by the research team, which contained information about CBT-I, sleep, and cancer survivorship.
    - They could engage with the website as they wished for six weeks, but there was no tailoring or interactive feedback provided.
- The primary outcome measured insomnia symptoms via the change in the scores on the ISI.
    - A decrease of seven points was considered moderate improvement, while an eight-point decrease marked significant improvement.
- Secondary outcomes were assessed using the CSD data from baseline and end-of-study.
- Participants used a sleep diary to track several sleep domains, including latency, total sleep time, and sleep efficiency.
    - Sleep quality was measured by a five-point Likert scale, and the average response was used for analysis.

        - A score of five was considered the highest while one was considered the lowest.
    - Total sleep time was calculated by subtracting the time awake (sleep onset latency and wake after sleep onset) from the total time in bed.
    - Sleep efficiency was the ratio of total sleep time to time in bed.

INTERVENTION (# IN THE GROUP): 38

COMPARISON (# IN THE GROUP): 38

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- CBT-I improved insomnia severity compared to web-based educational program at six weeks (mean difference [MD] 5.8; 95% CI, 3.8–7.8).

Secondary Outcome –

- CBT-I improved the following compared to a web-based educational program from baseline:
    - Sleep quality (MD 0.56; standard error [SE] 0.09; 95% CI, 0.39–0.74)
    - Sleep onset latency (MD 8.3 minutes; SE 3.3; 95% CI, 1.9–15)
- CBT-I resulted in minimal wakefulness after sleep onset compared to a web-based education program (MD 9.5 minutes; SE 3.9; 95% CI, 1.9–17).
- CBT-I resulted in slightly worse sleep efficiency compared to a web-based educational program (MD –0.04%; SE 0.01; 95% CI, –0.07 to –0.01).
- There was no statistically significant difference in total sleep time in the intervention group compared to the control group.

LIMITATIONS:

- The findings may not be fully generalizable to populations with different racial, ethnic, or educational backgrounds.
- The study duration was limited to six weeks.
- The study relied on self-reported sleep measures.

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