GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 27

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of July 3 - 7, 2023

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- Are Community Health Workers Effective in Maintaining Long-Term T2DM Self-Management?
- Recent Gout Flare Associated with Increased Rates of Cardiovascular Events

Could We Manage LUTS with Self-Management Methods?

Self-Management for Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-Analysis

Albarqouni L, Sanders S, Clark J, Tikkinen KAO, Glasziou P. Self-Management for Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-Analysis. *Ann Fam Med*. 2021;19(2):157-167. doi:10.1370/afm.2609.

KEY TAKEAWAY: Compared to usual care, self-management methods alone or in combination with drug therapy significantly reduce the severity of lower urinary tract symptoms (LUTS) among men.

STUDY DESIGN: Systematic review and meta-analysis of six randomized controlled trials (RCTs; N=1,006)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: LUTS affect a great number of men, and negatively impact their quality of life in significant ways. Self-management methods alone or with concurrent drug therapy may reduce the symptoms that, in return, improve quality of life.

PATIENTS: Men with LUTS

INTERVENTION: Self-management

CONTROL: Usual care or drug therapy alone

PRIMARY OUTCOME: Severity of LUTS

Secondary Outcome: Frequency of nocturia episodes and 24-hour period voiding episodes

METHODS (BRIEF DESCRIPTION):

- The mean age of participants across the RCTs was mid-60s, with a range of 36–83 years old. Other demographic information was not provided.
- Inclusion criteria: Men with LUTS, not due to infection, cancer, or prostate surgery
- The intervention group received 1–6 educational sessions spaced between one event to 10 years on various self-management methods.
  - These methods include education regarding pathophysiology, the natural course of LUTS, reassurance regarding prostate cancer, limiting caffeine fluid intake, and alcohol reduction.
- All the groups also received standard medication management.
- The control group received usual care, and standard drug therapy such as α-blocker (tamsulosin 0.4 mg daily), 5-α reductase inhibitor (finasteride 5 mg daily), antimuscarinic, and sedative-hypnotic agents.
- Outcome measurement:
  - LUTS were measured by validated scoring systems such as:
    - The International Prostate Symptom Score (IPSS), ranged from 0 to 35
    - American Urological Association Symptom Index (AUA-SI), ranged from 0 to 35
    - Higher scores indicated more severe disease burdens with both scales.
  - Frequency of nocturia episodes and 24-hour period voiding episodes, reported by participants.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Six weeks to six months

RESULTS:

- Compared to usual care, self-management significantly reduced the severity of LUTS at six months (2 RCTs, n=350; mean difference [MD] –7.4; 95% CI, –8.8 to –6.1; I^2=14%).
- Compared to usual care, the self-management group had significantly fewer:
  - Nocturia episodes (1 RTC, n=140; MD –0.60; 95% CI, –1.1 to –0.08)
  - 24-hour period voiding episodes (one RTC, n=140; MD –1.6; 95% CI, –2.9 to –0.30)
- In the self-management vs drug therapy group, there was no significant difference in the severity of LUTS between the two groups at 6–12 weeks.
- Compared to the drug therapy group, the self-management group had significantly fewer nocturia episodes (three RTCs, n=419; MD –0.42; 95% CI, –0.67 to –0.17; I^2=57%).
  - Did not demonstrate a difference in 24-hour period voiding episodes.
- In combined self-management and drug therapy vs drug therapy alone:
  - Combination significantly reduced the severity of LUTS at six weeks (1 RTC, n=204; MD –2.3; 95% CI, –4.1 to –0.49).
  - The combination group had significantly fewer nocturia episodes (2 RTCs, n=276; MD –0.45; 95% CI, –0.77 to –0.14).

- The combination group had significantly fewer 24-hour period voiding episodes (1 RTC, n=204; MD –2.1; 95% CI, –3.0 to –1.3).

LIMITATIONS:

- Unclear definition of self-management interventions in some trials.
- Duration of intervention (1–3 months) was short in the context of the course of LUTS symptoms in patients' lives.
- LUTS symptoms questionnaire did not capture the full spectrum of symptoms and their effect on patients' lives.

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Understanding Cardiovascular Risks of ADHD Medications

Risk of Cardiovascular Diseases Associated with Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis

Zhang L, Yao H, Li L, et al. Risk of Cardiovascular Diseases Associated with Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(11): e2243597. doi:10.1001/jamanetworkopen.2022.43597

KEY TAKEAWAY: There is no significant association between attention-deficit/hyperactivity disorder (ADHD) medication use and the risk of cardiovascular events across all age groups, although a modest risk increase cannot be excluded.

STUDY DESIGN: Systematic review and meta-analysis of 19 observational studies (N=3,931,532)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to observational studies with high heterogeneity)

BRIEF BACKGROUND INFORMATION: Although ADHD medications are effective in reducing core ADHD symptoms, there is concern about cardiovascular safety. Current practice guidelines recommend identifying individuals at cardiovascular disease (CVD) risk prior to initiating stimulant and non-stimulant ADHD medications and limiting their use in adults at higher risk, though it remains uncertain whether these medications lead to clinically significant cardiovascular risk over time. In this review, the authors examine the association between ADHD medications and poor CV outcomes.

PATIENTS: Patients with ADHD

INTERVENTION: Stimulant and non-stimulant ADHD medications

CONTROL: No intervention

PRIMARY OUTCOME: Cardiovascular disease

METHODS (BRIEF DESCRIPTION):

- Patients of all ages (age 3 to ≥74) with ADHD across six countries were included in the study.
  - 60.9% of study participants were male.
- Study interventions included amphetamines, atomoxetine, methylphenidate, guanfacine, and/or pemoline.
- Comparator group included ADHD patients with no intervention or to the general population without ADHD diagnosis.
- Primary CVD outcomes included hypertension, heart failure, cardiac arrest, tachyarrhythmias, myocardial infarction, and stroke.
- Outcomes were measured via a review of insurance claims and/or surveys.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Median 1.5 years (range 0.25–9.5)

RESULTS:

Primary Outcome –

- ADHD medication use was not associated with an increased risk of CVD events among children and adolescents, young adults, older adults, or overall.

Secondary Outcome –

- There was no association between ADHD treatment and CVD based on biological sex, though there was high heterogeneity between studies (male I^2= 96.1%, female I^2= 85.6%).
- There was no significant association between ADHD medications and CVD events among patients with or without a history of CVD (n=8 studies).
- Two studies with long-term follow-up found an associated increased risk with ADHD medications and CVD events (relative risk (RR) 2.0; 95% CI, 2.0–2.1 and RR 3.1; 95% CI, 1.1–8.6, respectively) in patients with CVD history.

LIMITATIONS:

- The studies had high and significant heterogeneity.
- Studies were at risk for immortal time bias due to potential misclassification of time intervals.
- Only two studies included long-term follow-up (>2.5 years), which may underestimate risk over time.
- ADHD medications cannot be individually compared as the intervention group was not separated by medication class (i.e., stimulant versus non-stimulant).
- There were few studies with data on dosage and duration of medication use, and thus it is impossible to quantify any dose-response association.
- The control group in several studies consisted of patients without ADHD diagnosis.

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Should We Be Restricting Fluid for Sepsis Induced Hypotension or Not?

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network, Shapiro NI, Douglas IS, et al. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. *N Engl J Med*. 2023;388(6):499-510. doi:10.1056/NEJMoa2212663

KEY TAKEAWAY: Restrictive fluid therapy with early vasopressor use does not decrease 90-day mortality compared to liberal fluid therapy in sepsis-induced hypotension.

STUDY DESIGN: Multi-center, randomized, unblinded, superiority trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to a significant number of limitations)

BRIEF BACKGROUND INFORMATION: Both vasopressor use and fluid resuscitation for sepsis-induced hypotension are popular and mainstay therapy options. However, there is little data and guidance on the use of early vasopressor use or continued fluid management of sepsis-induced hypotension.

PATIENTS: Adults with hypotension due to sepsis

INTERVENTION: Restrictive fluid strategy

CONTROL: Liberal fluid strategy

PRIMARY OUTCOME: All-cause death before discharge home or by day 90 from presentation

Secondary Outcome: Days free from end-organ support therapy at 28 days, days free from ventilator use at 28 days, days free from vasopressor use at 28 days, out of ICU at 28 days

METHODS (BRIEF DESCRIPTION):

- Participants were from the US (60 centers)
  - ≥18 years old
  - Confirmed or suspected infection and sepsis-induced hypotension with SBP <100 mmHg after 1 L of fluid
  - Identified within 4 hours of criteria being met for sepsis-induced hypotension
- Average participant:
  - 59.5 years old
  - 47.2% female
  - 70.7% white
  - 15.8% Black
- Exclusion criteria:
  - Diagnosed more than 24 hours after presentation
  - Received over 3L of fluid before diagnosis
  - Diagnosed with fluid overload
  - Sustained volume depletion from other causes
- Randomization via a web-based system was performed on a 1:1 ratio.
  - Restrictive fluid therapy (≤2 L initial bolus) with early norepinephrine use or epinephrin as a secondary vasopressor titrated until hypotension resolved and able to wean off vasopressors (dose adjusted after reassessment)
  - Liberal fluid therapy (>2 L initial bolus followed by repeated boluses of 500 mL until hypotension resolved)
- Protocols for both groups were followed for 24 hours.
  - Clinical teams could override protocols, if necessary, to treat the approach.
  - Protocol was monitored in the first 300 patients and then 10% random sampling.

INTERVENTION (# IN THE GROUP): 781

COMPARISON (# IN THE GROUP): 782

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- All-cause death before discharge home or by day 90 was similar in both groups.
  - 109 patients (14%) in the restrictive fluid group and 116 patients (15%) in the liberal fluid group
  - (Estimated difference, –0.9%; 95% CI, –4.4 to 2.6)

Secondary Outcome –

- Mean days free from end-organ support therapy at 28 days were similar for both groups.
- Mean days free from ventilator use at 28 days were similar for both groups.
- Mean days free from vasopressor use at 28 days were similar for both groups.
- Mean out of ICU at 28 days was similar for both groups.
- Mean days out of the hospital at 28 days were similar for both groups.

LIMITATIONS:

- Some patients received more or less fluid than intended in their respective groups, which could have biased observations.
- There was no assessment for specific subgroups with coexisting conditions that could benefit from one strategy over another.
- The study was unblinded, therefore it could have influenced the reporting of adverse events.
- There was no usual care group.
- Resuscitation targets were standardized whereas different targets might have been better for different participants.
- There was no assessment of the safety or effectiveness of the targets.
- The duration of therapy was only up to 24 hours.
- Enrollment of a population with higher severity of illness may have affected the outcomes.
- Sepsis-induced hypotension was recognized early (hospital presentation), and therefore, the outcomes cannot be generalized to patients later in their care.

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Are Community Health Workers Effective in Maintaining Long-Term T2DM Self-Management?

Community Health Workers as Trust Builders and Healers: A Cohort Study in Primary Care

Ferrer RL, Schlenker CG, Cruz I, et al. Community Health Workers as Trust Builders and Healers: A Cohort Study in Primary Care. *Ann Fam Med*. 2022;20(5):438-445. doi:10.1370/afm.2848

KEY TAKEAWAY: Community Health Workers aid in attaining better autonomous control of type 2 diabetes mellitus management.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Diabetes prevalence increased from less than 1% in 1958 to 11% in 2020 in U.S. adults. Patients living in socially disadvantaged communities suffer disproportionate amounts of diabetes complications if glycosylated hemoglobin, blood pressure, and serum lipids are uncontrolled. Several studies support the role of community health workers in chronic disease management but for short durations. The long-term impact, optimal design, and duration for the role of Community Health Workers in the management of uncontrolled type 2 diabetes mellitus is not clearly understood.

PATIENTS: Adults with type 2 diabetes mellitus

INTERVENTION: Self-management through community health workers

CONTROL: Not applicable

PRIMARY OUTCOME: HbA1c <9%

Secondary Outcome: Change in hemoglobin A1c, need for a visit to the hospital, emergency department (ED), or urgent care

METHODS (BRIEF DESCRIPTION):

- Adults (average age 52) from San Antonio, Texas Family and Community Medicine Practice Registry (1,270 eligible patients agreeable to meeting with a community health worker) with type 2 DM with HbA1c 9% or higher or clinicians' referrals were followed for four years.
- Through a series of in-person meetings, community health workers cycled through four questions to highlight patients' intended outcomes and motivations, create feasible approaches, and link these to intended outcomes.
    - Patients' intermediate goals included healthy food, sufficient activity, appropriate medication use, active participation in health care, understanding the numbers measuring self-management success, and developing trust in key partners.
- Community Health Workers identified three categories of care:
    1) Outreach: Consisted of patient and community health workers meeting in person
    2) Stabilization: Where patients and community health workers recognized and addressed self-care obstacles
    3) Self-care: Generativity when the motivation for self-care was displayed and techniques to manage diabetes in their home were performed
- Healthcare utilization outcomes were examined by counting data through pre- and post-intervention trends in visits to the ED, hospital, and urgent care.
    - Qualitative data from CHW stories were defined and described to address patients' progress to self-care generativity through three operationally defined periods of care (Outreach, Stabilization, Self-care Generativity)
- Investigators were blinded to HbA1c values and health services outcomes while defining the periods of care variables.
- Process variables for each patient: number of encounters with community health workers, time spent with community health workers, and community health worker's observation of each encounter.

INTERVENTION (# IN THE GROUP): 986

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 1,365 days

RESULTS:

Primary Outcome –

- Healthcare worker support, regardless of strategy, improved HbA1c from baseline through the fourth visit at a mean of 859 days.
    - Outreach: 10 vs 9.5 (P<.001)
    - Stabilization: 10 vs 9.6 (P<.001)

    - Self-care Generativity: 10 vs 9.4 (P<.001)
- Healthcare worker support, regardless of strategy, improved HbA1c from baseline through the tenth visit at a mean of >1365 days.
    - Outreach: 10 vs 8.8 (P <.001)
    - Stabilization: 10 vs 9.0 (P<.001)
    - Self-care Generativity: 10 vs 8.5 (P<.002)

Secondary Outcome –

- Health care utilization for emergency visits was increased in the stabilization (IRR 1.7; 95% CI, 1.4–2.4) and outreach (IRR 1.3; 95% CI, 1.0–1.8) group when compared to the self-care generativity group.
- Health care utilization for hospital visits was increased in the stabilization (IRR 2.1; CI 95%, 1.3–3.2) and outreach (IRR 1.1; 95% CI, 0.6–1.9) group when compared to the self-care generativity group.

LIMITATIONS:

- Accepting help from Community Health Workers may signal a desire to engage in health-promoting behaviors.
- The study's findings must be interpreted as quality improvement intervention instead of randomized control trial; thus results may be influenced by biases of nonrandomized intervention studies.

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Recent Gout Flare Associated with Increased Rates of Cardiovascular Events

Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients with Gout

Cipolletta E, Tata LJ, Nakafero G, Avery AJ, Mamas MA, Abhishek A. Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients with Gout. *JAMA*. 2022;328(5):440-450. doi:10.1001/jama.2022.11390

KEY TAKEAWAY: Gout flares significantly increase the risk of cardiovascular events in the first 120 days following a flare.

STUDY DESIGN: Nested case-control study and self-controlled case series

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Millions of people in the US have a diagnosis of gout. Gout is characterized by low-grade inflammation that may precipitate atherothrombosis leading to cardiovascular events. However, there is limited evidence examining the association between gout flares and cardiovascular events.

PATIENTS: Patients with a diagnosis of gout

INTERVENTION: Gout flare

CONTROL: No gout flare

PRIMARY OUTCOME: Cardiovascular event

METHODS (BRIEF DESCRIPTION):

- The study participants had a mean age of 76 years old, with 70% male, and a BMI of 28 was equal between the case and control groups.
  - History of cardiovascular diseases (stroke or heart attack) was higher at 52% in the case group, compared to 20% in the control group.
  - Inclusion criteria: Adults aged 18 and up with a recent diagnosis of gout who contributed data to the Clinical Practice Research Data Link in England for 24 years (January 1, 1997–December 31, 2020).
- A gout diagnosis was defined using a diagnostic code for gout flares used in the medical record, hospitalization with gout as a primary diagnosis, or primary care visit for gout with NSAIDs, steroids, or colchicine prescribed.
  - Cases were defined as patients with a cardiovascular event, i.e., acute MI (myocardial infarction) or stroke (ischemic or hemorrhagic) based on hospital records and primary care records.
- Matching: Up to five comparisons were matched with each case.
  - Age (± 2 years), sex, and length of time since a gout diagnosis (± 2 years) were used.
- For the self-controlled case series portion, patients had both gout flare exposure and a cardiovascular event.
- The exposure period of gout flares extended from 0–60, 61–120, 121–180, and 181–720 days.
- Cardiovascular event rates were compared before a gout flare and in the 180 days following the flare.

INTERVENTION (# IN THE GROUP): 10,475

COMPARISON (# IN THE GROUP): 52,347

FOLLOW-UP PERIOD: Case-control: 24 years, Self-controlled case series: 720 days (about 2 years)

RESULTS:

Primary Outcome –

- Compared to patients who didn't have cardiovascular events, patients with cardiovascular events had significantly higher rates of gout flares:
  - Within the prior 0–60 days (1.4 % vs 2.0%, respectively; adjusted odds ratio [aOR] 1.9; 95% CI, 1.5–2.4).
  - Within the prior 61–120 days (1.6% vs 1.2%, respectively; aOR 1.6; 95% CI, 1.3–2.0).
- There were no significant differences in the rate of gout flares in more than 121 days before cardiovascular events.

LIMITATIONS:

- Stroke types, such as ischemic or hemorrhagic, were not included.
- Cardiovascular or gout flare events in which a patient did not seek medical care were not included.
- The severity of gout was not considered.
- Limited generalizability: Unable to conclude if the association differed by race or ethnicity as these were not included as covariates.
- Surveillance bias might be introduced by patients who had previously had a cardiovascular event before the diagnosis of gout.

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