GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 36

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of September 6 - 10, 2021

SPOTLIGHT: Patient Navigation to Reduce Inpatient Readmission in Substance Use Disorder Patients

- Vitamin D, Not the Answer to All
- How Intensely Do You Exercise and Does It Make a Difference for Your Health?
- There's an App for Everything: Digital Intervention on Depressive Symptoms in Patients with Hypertension or Diabetes

Patient Navigation to Reduce Inpatient Readmission in SUD Patients

Preventing Hospital Readmission for Patients with Comorbid Substance Use Disorder: A Randomized Trial

Gryczynski J, Nordeck CD, Welsh C, Mitchell SG, O'Grady KE, Schwartz RP. Preventing Hospital Readmission for Patients with Comorbid Substance Use Disorder: A Randomized Trial. *Ann Intern Med*. 2021; 174(7):899–909. doi:10.7326/M20-5475

KEY TAKEAWAY: Navigation Services (NavSTAR) reduced inpatient readmissions and emergency department (ED) visits in hospitalized patients with comorbid substance use disorders.

STUDY DESIGN: Two-group parallel single-site randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Persistent use of hospital services reflects poor health and suboptimal care. It is also a primary consumer of health care dollars. Multicomponent care has been found to be effective in decreasing hospital readmissions, thus decreasing costs. Alcohol-related disorders are associated with the highest rates in hospital readmissions. Likewise, patients with opioid use disorder (OUD) have a higher risk of readmission after surgery.

PATIENTS: Adult hospital patients with opioid, cocaine, or alcohol use disorder

INTERVENTION: NavSTAR program

CONTROL: Treatment as usual (TAU)

OUTCOME: Unplanned inpatient readmission from all causes

Secondary Outcomes: Mortality, entry into treatment, urine drug measures of illicit drug use, HIV risk, and quality of life

METHODS (BRIEF DESCRIPTION):

- Patients were screened by hospital addiction service to determine if they met criteria from the Manual of Mental Disorders for opioid, cocaine, or alcohol use disorder.
- Patients were randomly assigned to NavSTAR or TAU.
  - NavSTAR included motivational interviewing, proactive case management, and care coordination to resolve barriers to care.
- TAU included counseling and withdrawal management, initiation of medication-assisted treatment, and referrals to community-based substance use disorder (SUD) treatment.
- Follow-up interviews were done at 3, 6, & 12 months after discharge.
- Cox regression was calculated to measure the association between treatment intervention and primary outcome.

INTERVENTION (# IN THE GROUP): 200

COMPARISON (# IN THE GROUP): 200

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- NavSTAR resulted in fewer inpatient readmissions than TAU (HR 0.74; 95% CI, 0.58–0.96).
- NavSTAR participants were less likely to have inpatient readmission within 30 days of discharge compared to the TAU group (16% vs 30%; OR 0.43; 95% CI, 0.26–0.70).

Secondary Outcomes –

- NavSTAR resulted in fewer ED visits than TAU (HR 0.66; 95% CI, 0.49–0.89).
- NavSTAR participants reported faster entry into SUD treatment than TAU participants (HR 1.4; 95% CI, 1.1–1.9).
- There was no difference in mortality between the two groups (HR 0.77; 95% CI, 0.44–1.4).
- The NavSTAR group had fewer opioid-positive urine drug tests (no data reported).
- There was no significant difference in the participant-reported quality of life or HIV risks (no data reported).

LIMITATIONS:

- The study location at a single, large, urban academic health center with established addiction service may make the results not generalizable to other populations.
- Small sample size.
- Follow up rates were lower than anticipated.
- Urine did not account for Fentanyl.
- Multicomponent intervention limited the ability to determine which element was the main contributing factor to improved outcomes.

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Vitamin D, Not the Answer to All

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med*. 2019; 380(1):33–44. doi:10.1056/NEJMoa1809944

KEY TAKEAWAY: Supplementation with 2,000 IU per day of vitamin D does not significantly reduce the incidence of cancer and cardiovascular events in men 50 years old and older and women 55 years old and older.
STUDY DESIGN: Double blind randomized placebo-controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The top two leading cause of death in the United States are cardiovascular disease and cancer. Some observational studies have demonstrated associations between low levels of vitamin D and increased risks of cardiovascular disease and cancer. However, prior research on supplementation with vitamin D to prevent these diseases has been limited.

PATIENTS: Men 50 years old and older and women 55 years old and older
INTERVENTION: 2,000 IU of oral vitamin D_3 and 1 g of omega-3 fatty acids per day
CONTROL: Placebo
OUTCOME: Invasive cancer of any kind and major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes)
Secondary Outcomes: Site-specific cancers including colorectal, breast and prostate cancer, death from cancer, and additional cardiovascular events

METHODS (BRIEF DESCRIPTION):

- 25,871 participants in the United States from various races with no prior history of cancer (except non-melanoma skin cancer) or cardiovascular disease were randomly assigned to receive 2,000 IU of vitamin D_3 and 1 g of omega-3 fatty acids or a placebo to take once per day after a 3-month placebo run-in phase.
- All participants completed questionnaires at the beginning of the study to gather information on risks of cancer and cardiovascular disease and food intake frequency.
- They also completed follow-up questionnaires after randomization at six months, one year, and then annually to assess for developments of major illness, compliance with study regimen, outside use of vitamin D supplements, new risk factors for measured outcomes, and potential side effects.
- All willing participants of the study (16,956) offered blood samples to assess their baseline vitamin D level.
- Participants or family members self-reported endpoint events which were verified through their medical records and histology or cytology for cancers.
- If a participant passed during the study period, records were received from the National Death Index if medical records were unavailable.

INTERVENTION (# IN THE GROUP): 12,927
COMPARISON (# IN THE GROUP): 12,944

FOLLOW UP PERIOD: Median 5.3 years

RESULTS:
Primary Outcomes –

- There was no statistically significant difference in the rate of developing invasive cancer between the vitamin D and placebo groups (Hazard Ratio [HR] 0.96; 95% CI, 0.88–1.1).
- There was no statistically significant difference in the incidence of a major cardiovascular event between the vitamin D and placebo groups (HR 0.97; 95% CI, 0.85–1.1).

Secondary Outcomes –

- There were no significant differences between the two groups studied in the incidence of:
  - Breast cancer (HR 1.0; 95% CI, 0.79–1.3);
  - Prostate cancer (HR 0.88; 95% CI, 0.72–1.1); or
  - Colorectal cancer (HR 1.1; 95% CI, 0.73–1.6).
- There were no significant differences in cumulative cardiovascular events (including coronary revascularization and coronary artery bypass grafting) between the two groups (HR 0.96; 95% CI, 0.96–1.1).
- There were no significant differences in the diagnosis of hypercalcemia, kidney stones, or gastrointestinal symptoms between the intervention and control group.

LIMITATIONS:

- This study only tested one dose of vitamin D. Results might have been different if a higher dose of vitamin D was compared to the control. Higher levels of vitamin D might be needed to see a reduction in the incidence of cancer and cardiovascular events.
- Most participants in this study were only followed for about 5 years (median follow-up 5.3 years). This is a short time considering the risk for cancer and cardiovascular events tend to increase with age.

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How Intensely Do You Exercise and Does It Make a Difference for Your Health?

Association of Physical Activity Intensity with Mortality: A National Cohort Study

Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of Physical Activity Intensity With Mortality: A National Cohort Study of 403 681 US Adults. *JAMA Intern Med.* 2021; 181(2):203–211.

KEY TAKEAWAY: A higher proportion of vigorous physical activity to total physical activity is associated with lower overall mortality.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Guidelines recommend various amounts of physical activity for adults. It is unknown whether vigorous, or high intensity, activity is associated with reduced mortality.

PATIENTS: Civilian adults in the United States

INTERVENTION: Vigorous physical activity

CONTROL: Light/moderate physical activity

OUTCOME: All-cause mortality, cardiovascular disease mortality, and cancer mortality

METHODS (BRIEF DESCRIPTION):

- 403,681 participants from 35,000 selected households from CDC's National Health Survey chosen from stratified randomized clusters.
- Exclusion criteria included missing physical activity information, disabilities, inability to perform moderate-vigorous activity, and baseline heart disease, cancer or stroke.
- Two sets of questions monitoring frequency of >10 minutes of exercise and duration for both light activity and vigorous activity.
    - Light activity was defined as activity only causing light sweating or slight increase in breathing or heart rate.
    - Activity was defined as vigorous if it caused heavy sweating or large increase in breathing or heart rate.
- Frequency and duration were multiplied to get total amount of moderate and vigorous activity.

INTERVENTION (# IN THE GROUP): 493,365

COMPARISON (# IN THE GROUP): 403,681

FOLLOW UP PERIOD: 2 to 18 years

RESULTS: A greater proportion of vigorous physical activity to total physical activity was associated with lower overall mortality but had no association with lower cancer mortality or cardiovascular disease.

- When compared to participants with 0% vigorous physical activity, participants with 50% or more vigorous physical activity had lower age-standardized all-cause mortality (HR 0.83; 95% CI, 0.78–0.88).

LIMITATIONS:

- Participants' data on physical activity was from self-reported questionnaires allowing for recall bias.

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There's an App for Everything: Digital Intervention on Depressive Symptoms in Patients with Hypertension or Diabetes

Effect of a Digital Intervention on Depressive Symptoms in Patients with Comorbid Hypertension or Diabetes in Brazil and Peru: Two Randomized Clinical Trials

Araya R, Menezes PR, Claro HG, et al. Effect of a Digital Intervention on Depressive Symptoms in Patients With Comorbid Hypertension or Diabetes in Brazil and Peru: Two Randomized Clinical Trials. *JAMA*. 2021; 325(18):1852–1862. doi:10.1001/jama.2021.4348

KEY TAKEAWAY: A digital intervention significantly improved depression symptoms in depressed patients with comorbid hypertension or diabetes at 3 months.
STUDY DESIGN: Cluster randomized clinical trial (RCT) at 20 sites in São Paulo, Brazil and an individual-level RCT at 7 sites in Lima, Peru
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Depression is a common comorbidity for patients with hypertension or diabetes. Untreated depression has been associated with decreased patient compliance and care outcomes. Treating depression in these patients would improve outcomes, but there is a significant gap between the number of trained mental health providers and patients with depression. Digital interventions, with human support, potentially provide an effective and scalable solution to filling this treatment gap.

PATIENTS: Adults with a diagnosis of diabetes or hypertension who screened positive for depressive symptoms
INTERVENTION: Brief automated therapy sessions via smartphone based digital app, in addition to usual care
CONTROL: Usual care for depression at the discretion of the primary provider
OUTCOME: 50% reduction in PHQ-9 scores at 3 months
Secondary Outcomes: 50% reduction in PHQ-9 scores at 6 months; assessment scores for quality of life, disability, behavioral activation, and health care service utilization at 3 and 6 months

METHODS (BRIEF DESCRIPTION):

- Adults (≥21 years) with a PHQ-9 score ≥10 and who reported receiving treatment for hypertension and/or diabetes were recruited from São Paulo, Brazil and Lima, Peru. Patients at high risk of suicide and who had pregnancy associated diabetes and/or hypertension were excluded.
- The treatment group received 18 therapy sessions over 6 weeks based on behavioral activation principals through a digital app on a smartphone, which was supported remotely by nurse assistants. Each session was less than ten minutes and conducted three times a week.
  - Content was an evidence based psychological approach to treat depression.
- The control group received usual care, as determined by their primary physician, for similar duration. Usual care was not defined and at the discretion of the primary physician.
- Outcomes were measured at 3 and 6 months after completing the intervention.
  - Primary outcome was improvement of depression symptoms indicated by a 50% reduction or more on baseline PHQ-9 scores.
  - Secondary outcomes were improvements for the following assessments:
    - Quality of life was measured by the 3-level version of the Euroqol Group Quality of life assessment (EQ-5D-3L; scale 5–15).
    - Disability was assessed with the World Health Organization Disability Assessment Schedule-II (WHODAS-II; scale 0–48).
    - Behavioral activation was assessed with the Behavioral Activation for Depression Scale-Short Form (BADS-SF; scale 0–54).
    - Health care service utilization was assessed based on the number of health service consultations, hospital admissions, and home visits by primary care teams.

INTERVENTION (# IN THE GROUP): 657 (440 at São Paulo; 217 at Lima)
COMPARISON (# IN THE GROUP): 655 (440 at São Paulo; 215 at Lima)

FOLLOW UP PERIOD: 19 months

RESULTS:
Primary Outcome:

- Participants with at least 50% reduction of baseline PHQ-9 scores at 3 months with digital application intervention vs control group:

    - São Paulo: 40.7% vs 28.6% (between-group absolute difference 12%; 95% CI, 5.5 to 19)
    - Lima: 52.7% vs 34.1% (absolute difference 19%; 95% CI, 9.1 to 28)

Secondary outcomes of digital app intervention vs usual care:

- There was no significant improvement of depressive symptoms as assessed by PHQ-9 at 6 months.
- Improvement in quality of life at 3 months (mean difference [MD] 0.03;95% CI, 0.01 to 0.05)
- Decreased disability at 3 months (MD –2.6; 95% CI, –4.8 to –0.40]
- Increased behavioral activation at 3 months (MD 3.3; 95% CI, 2–5.3) and 6 months (MD 2.2; 95% CI, 0.4–3.9)
- Mean number of medical consultations, hospitalizations, and home visits
- No significant changes in number of medical consultation, hospitalizations, or home visits at 3 and 6 months.

LIMITATIONS:

- Both RCTs conducted in South American countries, which potentially limits generalizability of findings across cultures.
- Both RCTs targeted low socio-economic patient populations, limiting generalizability to higher socio-economic groups.
- The principal investigator of both RCTs disclosed a pending patent for CONEMO, the digital app used in both RCTs.

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