GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of March 13 - 17, 2023

SPOTLIGHT: Little Nutrients for Big Diseases

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Little Nutrients for Big Diseases

Vitamin and Mineral Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: Updated Evidence Report and Systematic Review for the US Preventative Services Task Force

O'Connor EA, Evans CV, Ivlev I, et al. Vitamin and Mineral Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2022;327(23):2334-2347. doi:10.1001/jama.2021.15650

KEY TAKEAWAY: Micronutrients (e.g., Vitamin A, C, D, and E, beta carotene) supplementation does not improve prevention of any cancer or cardiovascular disease (CVD). Paradoxically, beta carotene supplementation increases the risk for lung cancer.

STUDY DESIGN: Systematic review and meta-analysis of 84 randomized controlled trials and cohort studies (N=729,803)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Because CVD and cancer are the two leading causes of death in the US, there have been a variety of proposed prevention strategies. The U.S. Preventive Services Task Force (USPSTF) seeks evidence for micronutrient supplementation in healthy adults to prevent both.

PATIENTS: Healthy adults

INTERVENTION: Vitamin and mineral supplementation

CONTROL: No supplementation/placebo

PRIMARY OUTCOME: CVD and cancer

METHODS (BRIEF DESCRIPTION):

- Participants were 65% female, and the mean age of the participants was 61 years old. Most participants were White.
- Trials rated as "poor" quality rating, indicating at least one fatal bias assessed by two reviewers utilizing six USPSTF design-specific criteria, were excluded.
- The intervention group received vitamins/minerals (multivitamins, 20 to 50 mg of beta carotene, 25,000 IU of vitamin A, 50 to 300 mg of vitamin E with or without 200 µg of selenium, 500 mg of vitamin C, 20 to 2,000 IU vitamin D with or without 1,000 to 1,200mg calcium), while the control group received placebo or no intervention.
- The outcomes included percentage with CVD or any cancer events.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Six months to 12 years

RESULTS:

- Multivitamin use did not reduce CVD or cancer (9 RCTs, n=51,550; odds ratio [OR] 0.94; 95% CI, 0.87–1.01; I^2=0%).
- Vitamin D (with or without calcium) use did not reduce:
  - CVD (7 RCTs, n=74,295; OR 1.0; 95% CI, 0.95–1.1; I^2=0%)
  - Cancer (19 RCTs, n=86,899; OR 0.98; 95% CI, 0.92–1.03; I^2=0%)
- Vitamin E use did not reduce:
  - CVD (4 RCTs, n=62,136; OR 0.96; 95% CI, 0.90–1.04; I^2=0%)
  - Cancer (5 RCTs, n=76,777; OR 1.02; 95% CI, 0.98–1.1; I^2=0%)
- Beta carotene use significantly increased risk for:
  - Lung cancer (4 RCTs, n=94,830; OR 1.2; 95% CI, 1.01–1.42; I^2=39%)
  - CVD (5 RCTs, n=94,506; OR 1.1; 95% CI, 1.02–1.19; I^2=0%)

LIMITATIONS:

- Difficult to control confounding variables, including amounts of vitamins and minerals within diverse diets of participants.
- Wide variation in follow-up time.
- Predominantly white population.
- Some of the trials were underpowered.

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The opinions and assertions contained herein are those of the author 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.

Improving Glycemic Goals with Intermittent Device Checks

Intermittently Scanned Continuous Glucose Monitoring for Type 1 Diabetes

Leelarathna L, Evans ML, Neupane S, et al. Intermittently scanned continuous glucose monitoring for type 1 diabetes. *N Engl J Med*. 2022;387(16):1477-1487.

KEY TAKEAWAY: Intermittently scanned continuous glucose monitoring (CGM) improves HbA1c levels more in patients with type 1 diabetes mellitus (T1DM) more than routine fingerstick testing.

STUDY DESIGN: Randomized, non-blinded, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Managing blood glucose levels in T1DM is paramount in preventing short- and long- term complications of diabetes. CGMs are more convenient and less painful than traditional fingerstick testing. Prior trials have compared efficacy of real-time CGM and first generation intermittent CGM against fingerstick testing. Second generation CGMs have additional alarm settings for high or low glucose levels available for use. This study evaluates the efficacy of second generation intermittently scanned CGM in reducing glycosylated HbA1c levels compared with fingerstick testing.

PATIENTS: Patients with T1DM

INTERVENTION: CGM with optional alarms

CONTROL: Fingerstick testing

PRIMARY OUTCOME: HbA1c levels

Secondary Outcome: HbA1c <7.5%, reduction of HbA1c, time to goal level, duration of hypoglycemia and hyperglycemia, glucose variability, patient satisfaction

METHODS (BRIEF DESCRIPTION):

- Participants were at least 16 years old with at least one year history of T1DM, HbA1c levels between 7.5% and 11%, using either continuous subcutaneous insulin infusion or multiple daily injections.
  - Exclusion criteria: pregnancy, current or prior use of real-time or intermittently scanned CGM, and complete loss of awareness of hypoglycemia as judged by investigators.
- All patients received 10–14 days of blinded CGM prior to randomization for baseline data.
- Patients were randomized into either group.
  - Intermittent CGM with optional alarms for high or low glucose
  - Routine fingerstick testing
- HbA1c levels were screened at 12 weeks and at 24 weeks.
- Six trial visits were held for all participants.
- The control group had 7th visit to obtain CGM blinded data for the last two weeks.
- Questionnaires at start and end assessing monitoring satisfaction via:
  - Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores range from 0-36 with greater satisfaction with higher scores.
  - Glucose Monitoring Satisfaction Survey (GMSS) scores range from 1-5, with greater satisfaction with higher scores.

INTERVENTION (# IN THE GROUP): 78

COMPARISON (# IN THE GROUP): 78

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- CGMs significantly improved HbA1c compared to fingerstick testing (7.9% vs 8.3%; adjusted Odds Ratio [aOR] –0.5; 95% CI, –0.7 to –0.3).

Secondary Outcome –

- Compared to fingerstick testing, CGMs significantly:
  - Reduced HbA1c levels to <7.5% (36% vs 22%; aOR 2.5; 95% CI, 1.1–5.7)
  - Reduced HbA1c levels by <5% (64% vs 30%; aOR 4.7; 95% CI, 2.1–11).
  - Reduced HbA1c levels by <1% (35% vs 12%; aOR 4.3; 95% CI, 1.7–11)
  - Increased time in glucose rage (9% longer; 95% CI, 4.7–13)
  - Reduced time spent hypoglycemic (3% less; 95% CI, 1.4–4.5)
  - Reduced time spent hyperglycemic (6% less; 95% CI, 0.9–11)
  - Reduced glucose variability (3.5% less; 95% CI, 1.8–5.3)
  - Improved patient satisfaction
    - 7 points higher in DTSQ (95% CI, 5.2–8.7)
    - 0.7 points higher in GMSS (95% CI, 0.5–0.9)

LIMITATIONS:

- The groups were not blinded.
- Most of the patients were White (97%).
- HbA1C levels were tested at home rather than a standardized lab due to the pandemic.
- The frequency of scanning or fingerstick testing was not reported.
- Patient-set alarm settings and utilization patterns were not available for analysis.
- Higher risk patients with recurrent hypoglycemia were excluded so the results have limited generalizability.

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Pharmacologic OPTIONS for Diabetic Peripheral Neuropathic Pain: Amitriptyline, Duloxetine, Pregabalin

Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial

Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial [published correction appears in *Lancet*. 2022 Sep 10;400(10355):810]. *Lancet*. 2022;400(10353):680-690. doi:10.1016/S0140-6736(22)01472-6

KEY TAKEAWAY: Monotherapies of pregabalin (P), amitriptyline (A), or duloxetine (D) result in similar and significant pain reduction for diabetic peripheral neuropathy. Combination therapy results in additional pain reduction in patients who failed monotherapy. Combination therapy is well tolerated with minimal significant adverse effects, which were well known to these medications and similar to monotherapy.

STUDY DESIGN: Multicenter, randomized, double-blind crossover study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Diabetic peripheral neuropathic pain is a growing issue with an increasing number of patients with diabetes and poor control of blood sugar. International guidelines recommend A, D, P, and gabapentin as first-line pain management. However, combination therapy has not been thoroughly assessed.

PATIENTS: Adults with diabetic neuropathy

INTERVENTION: Monotherapy, combination therapy, and combination pairs of A, P, and D

CONTROL: Not applicable

PRIMARY OUTCOME: Pain

METHODS (BRIEF DESCRIPTION):

- Participants were randomly assigned to one of the six permutations of medication combinations.
  - A-P -> D-P -> P-A
  - A-P -> P-A -> D-P
  - D-P -> A-P -> P-A
  - D-P -> P-A -> A-P
  - P-A -> D-P -> A-P
  - P-A -> A-P -> D-P
- Patients were masked to treatment pathways and medications. Treating physicians were masked to pathways but not medication dosing.
- During the first phase, patients would receive monotherapy for six weeks.
- Baseline mean pain score was 6.6 (SD 1.5) amongst participants.
- The seven-day daily pain scores were averaged at week six. Pain scores were assessed based on numerical rating scales of 0 indicating “no pain” and 10 indicating “worst pain imaginable”.
- Pain scores ≤3 were classified as responders and continued on monotherapy for additional 10 weeks.
- Pain scores >3 were classified as non-responders and started on the second medication for additional 10 weeks.
- The seven-day daily pain scores were measured and averaged at week 16.
- After 16 weeks, all medications were discontinued, and patients had a one-week washout period.
- This was repeated two more times for the following pairs in the assigned sequences.

INTERVENTION (# IN THE GROUP): 130

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 50 weeks

RESULTS:

Primary Outcome –

- Overall, all arms of treatment pathways resulted in similar and significant pain reduction.
  - Pairwise contrasts of the combination interventions had no statistically significant differences.
  - At week six, mean pain reduction across all pathways (monotherapies) was 2.6 (98.3% CI, 2.2–3.0; n=299; *P*<.0001) with a mean pain score of 3.9.
  - Mean maximum tolerated doses of monotherapy per day at week six were 56 mg for amitriptyline, 76 mg for duloxetine, and 397 mg for pregabalin.

- Combination therapy was effective for additional pain management when patients failed monotherapy.
- At week 16, mean pain reduction across all pathways was 3.4 (98.3% CI, 2.9 to 3.8; n=265; *P*<.0001) with a mean pain score of 3.3.
- Between weeks six and 16, responders (pain scores ≤3 at week 6), those who continued on monotherapy did not have further pain reduction of 0.2 (98.3% CI, –0.1 to 0.5).
- Between weeks six and 16, non-responders (pain scores >3 at week 6) started on combination therapy had further pain reduction of 1.0 (98.3%, CI 0.6 to 1.3).

LIMITATIONS:

- High attrition due to long study duration and limited follow-up during COVID-19.
- Short washout period between medications without taper to mitigate withdrawal symptoms and may not allow patients to return to baseline pain.

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Can Carpal Tunnel Syndrome Be Effectively Treated with Carpal Ligament Stretching?

Effective Self-Stretching of Carpal Ligament for the Treatment of Carpal Tunnel Syndrome: A Double-Blind Randomized Controlled Study

Shem K, Wong J, Dirlikov B. Effective self-stretching of carpal ligament for the treatment of carpal tunnel syndrome: A double-blinded randomized controlled study. *J Hand Ther*. 2020;33(3):272-280. doi: 10.1016/j.jht.2019.12.002

KEY TAKEAWAY: Stretching of the carpal ligament may improve symptom severity in patients with carpal tunnel syndrome.

STUDY DESIGN: Randomized, double-blinded, controlled study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high dropout rate resulting in small sample size)

BRIEF BACKGROUND INFORMATION: Carpal tunnel syndrome is a common neuropathology with a prevalence of 10% worldwide. Various treatment modalities exist with just as variable results. There is some evidence that manipulative therapy may decrease carpal tunnel pressure and therefore improve carpal tunnel syndrome.

PATIENTS: Patients with carpal tunnel syndrome

INTERVENTION: Self-performed myofascial stretching of the carpal ligament

CONTROL: Sham massage procedure

PRIMARY OUTCOME: Symptoms, functional severity, nerve conduction

METHODS (BRIEF DESCRIPTION):

- Patients 31–66 years old with median mononeuropathy were recruited from an electrodiagnostic medicine clinic.
- Patients with peripheral neuropathy, consistent use of adaptive equipment such as canes or wheelchairs, and inability to provide consent in English were excluded.
- Patients and researchers were both blinded and randomized to self-myofascial stretching of the carpal ligament or sham treatment.
- Symptomatic and functional severity were assessed at baseline and after six weeks. The neuropathic status of carpal tunnel syndrome was assessed using:
  - Visual Analog Scale (VAS) for wrist pain, hand numbness, hand tingling, and hand pain. Higher scores on the VAS correlated with increased symptom severity.
  - Symptom Severity Scale (SSS) and Functional Severity Scale (FSS): Responses to the SSS and FSS were scored on a scale of 1 to 5 with lower scores representing no symptoms or normal function.
  - Nerve conduction assessed sensory and motor distal latencies and amplitudes at baseline and six-week follow-up. Decreases in the distal latencies and increases in the amplitudes constitute improvements.
  - Pinch and grip strength: Calculated on the affected side by averaging.
- Each outcome measure was assessed using rmANOVA to detect any statistically significant differences.

INTERVENTION (# IN THE GROUP): 19

COMPARISON (# IN THE GROUP): 17

FOLLOW-UP PERIOD: Six weeks

RESULTS:

- Compared to sham treatment, self-myofascial stretching of the carpal ligament significantly improved:
  - Numbness (5.5 vs 4.2, respectively; *P*=.011)
  - Tingling (5.3 vs 4.1, respectively; *P*=.007)
  - Pinch strength (6.9 vs 8.4, respectively; *P*=.007)
  - Sensory amplitude (32 vs 23, respectively; *P*=.021)
  - Symptom severity (29 vs 27, respectively; *P*=.007)
- Sham treatment improved sensory distal latency more than self-myofascial stretching (4.7 ms vs 4.9 ms, respectively; *P*=.018).
- There were no significant differences in wrist pain, hand pain, grip strength, motor distal latency, motor amplitude, and FSS.

LIMITATIONS:

- There was a large rate of dropout which resulted in a small sample size.

- Concurrent use of NSAIDs and/or Orthosis was not controlled for in this study, as a result, there may have been a confounding effect on the results.

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Association Between COVID-19 Infection, Venous Thromboembolism, and Bleeding

Risks of Deep Vein Thrombosis, Pulmonary Embolism, and Bleeding after COVID-19: Nationwide Self-Controlled Cases Series and Matched Cohort Study

Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022;377:e069590. Published 2022 Apr 6. doi:10.1136/bmj-2021-069590

KEY TAKEAWAY: COVID-19 is a risk factor for deep vein thrombosis (DVT), pulmonary embolism (PE), and bleeding.

STUDY DESIGN: Self-controlled case series and cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Previous research presented conflicting data regarding the incidence of venous thromboembolism (VTE) after COVID-19. While increased VTE risk may prompt routine thromboprophylaxis in patients with COVID-19, this increases the risk of bleeding complications. Further research is needed to direct diagnostic and prophylactic strategies for VTE in COVID-19, particularly in non-severe cases.

PATIENTS: Adults living in Sweden

INTERVENTION: COVID-19 diagnosis

CONTROL: No COVID-19 diagnosis

PRIMARY OUTCOME: Diagnosis of DVT, PE, or bleeding event

METHODS (BRIEF DESCRIPTION):

- Patient-level data were queried from the communicable disease surveillance system SmiNet, the Public Health Agency of Sweden from February 2020–May 2021.
- Only the first infections were included.
- A self-controlled case series study was used to determine the incidence rate ratio for first VTE or bleeding events during the risk periods 1–7, 8–14, 15–30, 61–90, and 91–180 days post-COVID as compared to the reference timeframe (≥30 days before infection).
- In a matched cohort study, one COVID-19 case was matched to four controls based on age, sex, and country of residence.
- Individuals infected with COVID were 49% male, with a mean age of 40.2 years, 1.9% had a previous thromboembolic event (vs 1.6% in control), and 5.8% had a previous bleeding event (vs 4.9% in control).
- Outcomes included International Classification of Diseases (ICD)-9 and ICD-10 codes DVT, PE, and bleeding as a reason for contact in the outpatient or inpatient setting from data collected 30 days after COVID-19 diagnosis in the matched cohort study.
- Confounders used in the adjusted risk ratio included cancer, surgery, long-term anticoagulation, and a previous VTE event.

INTERVENTION (# IN THE GROUP): 1,057,174

COMPARISON (# IN THE GROUP): 4,076,342

FOLLOW-UP PERIOD: 30–180 days

RESULTS:

Primary Outcome –

- In the self-controlled case series analysis, the incidence rate for the first PE was 36 (95% CI, 32–41) during the 1st week after COVID-19 and 46 (95% CI, 41–53) during the second week as compared to the reference timeframe.
- During days 1–30 after COVID-19 as compared to the reference timeframe, incidence ratios were 5.9 (95% CI, 5.1–6.8) for DVT, 32 (95% CI, 28–36) for PE, and 2.5 (95% CI 2.3–2.) for bleeding.
- In the matched cohort study, adjusted risk ratios for the first DVT during 1–30 days after COVID-19 were 5.0 (95% CI, 4.96–5.01) for DVT, 33 (95% CI, 32.8–33.3) for PE, and 1.9 (95% CI 1.7–2.0) for bleeding.
- Using matched cohort data, the absolute risk among patients with COVID-19 as compared to the control group was 0.039% vs 0.007% for DVT, 0.17% vs 0.004% for pulmonary embolism, and 0.10% vs 0.04% for bleeding.

LIMITATIONS:

- Registry-based data may have been incomplete or inaccurate.

- Thromboembolism may have been underdiagnosed in COVID-19 patients who were critically ill or unstable for venous thromboembolism workup.
- Vaccine data was unavailable during the study.

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Does COVID-19 Cause Maternal or Fetal Complications?

Perinatal Complications in Individuals in California with or Without SARS-CoV-2 Infection During Pregnancy

Ferrara A, Hedderson MM, Zhu Y, et al. Perinatal Complications in Individuals in California With or Without SARS-CoV-2 Infection During Pregnancy. *JAMA Intern Med*. 2022; 182(5): 503-512.
Doi:10.1001/jamainternmed.2022.0330

KEY TAKEAWAY: COVID-19 during pregnancy is associated with an increased risk of maternal and fetal complications, including preterm birth and venous thromboembolism.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There are few studies that demonstrate how the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, the virus that causes the disease COVID-19, impacts maternal and fetal health during pregnancy. These prior studies found a link between preterm birth and COVID-19. The authors performed this study to better understand the health risk of COVID-19, from preconception through delivery.

PATIENTS: Pregnant patients who had a live or stillbirth

INTERVENTION: SARS-CoV-2 infection during pregnancy

CONTROL: No SARS-CoV-2 infection during pregnancy

PRIMARY OUTCOME: Maternal and fetal outcomes

METHODS (BRIEF DESCRIPTION):

- All pregnant patients in the Kaiser Permanente Northern California Healthcare system who had a live or stillbirth, as obtained from the Electronic Health Record (EHR) from March 1, 2020 through March 16, 2021.
- The mean age was 30.7 years old, with a standard deviation of 5.2 years.
- The patients self-reported as American Indian/Alaskan Native (0.3%), Asian/Pacific Islander (25.9%), Black (6.5%), Hispanic (28.4%), White (33.8%), and Multiracial/Unknown (5.0%).
- The patients with SARS-COV-2 were more likely to be <30 years old, identify as Hispanic, and have a diagnosis of obesity.
- Patients were tested for SARS-Cov-2 virus at admission for delivery via Polymerase Chain Reaction (PCR) testing.
- PCR testing data also included patients who tested positive 30 days prior to the last menstrual period, throughout the pregnancy, and seven days after delivery.
- Patients with a positive PCR test were included in the COVID-19-positive group.
- Patients with negative PCR testing or not tested for COVID-19 and without an ICD-10 code for COVID-19 were considered unexposed (or the control group).
- Maternal outcomes of interest were severe maternal morbidity and venous thromboembolism (VTE).
- Maternal morbidity included 21 conditions, such as acute renal failure, sepsis, pre-eclampsia, eclampsia, and acute myocardial infarction.
- Fetal outcomes of interest were preterm birth, as classified as delivery <37 weeks gestation.
- Preterm birth was further classified as early (22–31 weeks), moderate (32–33 weeks), and late pre-term birth (34–36 weeks).

INTERVENTION (# IN THE GROUP): 1,332

COMPARISON (# IN THE GROUP): 42,554

FOLLOW-UP PERIOD: From last menstrual period to delivery or outcome of interest

RESULTS:

Maternal Outcomes –

- Pregnant patients with SARS-CoV-2 infection were more likely to have severe maternal morbidity than those without SARS-CoV-2 infection (adjusted hazard ratio [aHR] 2.5; 95% CI, 1.9–3.1).
- There was a higher risk of VTE in the exposed group as compared to the unexposed group (aHR 3.1; 95% CI, 1.1–8.7).
- Co-morbid conditions, including pre-pregnancy obesity, chronic hypertension, and pregestational diabetes did not influence the strength of the associations.
- There was no association between SARS-CoV-2 infection and an increased rate of cesarean delivery.

Fetal Outcomes –

- There was a higher risk of preterm birth in those with SARS-CoV-2 during pregnancy, as compared to those without SARS-CoV-2 during pregnancy (aHR 2.1; 95% CI, 1.8–2.5).
- The association was strongest for early preterm birth (aHR 2.5; 95% CI, 1.5–4.2), and less for moderate preterm birth (aHR 2.2; 95% CI, 1.3–3.8) and late preterm birth (aHR 2.0; 95% CI, 1.6–2.4).

LIMITATIONS:

- Although patients were tested using PCR testing, a more accurate test than the rapid antigen testing, there is still the concern of false negatives and asymptomatic carriers.
- Potential for increased medical intervention with patients who tested positive for SARS-CoV-2.
- Symptom severities were not considered.
- Incomplete capture of potential confounding variables from health record data.

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What is the Best Approach When Treating Hypertension?

Adding a New Medication Versus Maximizing Dose to Intensify Hypertension Treatment in Older Adults

Aubert C, Sussman J, Hofer T, Cushman W, Ha J, Min L. Adding a new medication versus maximizing dose to intensify hypertension treatment in older adults: A retrospective observational study. *Ann Intern Med*. 2021;174(12):1666-1673. doi: 10.7326/M21-1456.

KEY TAKEAWAY: In patients with hypertension, adding a new medication is associated with a greater reduction in systolic blood pressure.

STUDY DESIGN: Retrospective observational cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to disease-oriented outcome)

BRIEF BACKGROUND INFORMATION: Two strategies to intensify blood pressure management exist: adding a new medication or maximizing dose. Evidence shows that both intensifications of treatment are beneficial even in older adults. Currently, no specific approach is supported in the outpatient setting in North America.

PATIENTS: Older adults with treated hypertension

INTERVENTION: Addition of a new anti-hypertensive medication

CONTROL: Increased dose of current anti-hypertensive

PRIMARY OUTCOME: Intensification sustainability, mean change in systolic blood pressure

METHODS (BRIEF DESCRIPTION):

- Patients included were ≥65 years with Veteran's Affair (VA) PCP (primary care physician) and hypertension on at least one anti-hypertensive not at maximum dose.
- Patients nearly all males; fewer than 2% of participants were female.
- Approximately 9% of patients smoked, 31% had diabetes, 14% had heart failure, and 31% had cardiovascular, cerebrovascular, or peripheral vascular disease.
- Patients were divided into a treatment group who received a new anti-hypertensive drug versus the control group who had a dose increase of their current anti-hypertensive drug.
- Dose and frequency of anti-hypertensives varied.
- Data was collected using VA pharmacy records, Medicare Part D medication files, and administrative and clinical data from encounters with PCP at VA.
- Baseline differences were adjusted with propensity score matching.
- Investigators assessed intensification sustainability (defined as ability to stay on new medication/dose) and change in systolic blood pressure (SBP) at three and 12 months.

INTERVENTION (# IN THE GROUP): 45,575

COMPARISON (# IN THE GROUP): 132,987

FOLLOW-UP PERIOD: 12 months

RESULTS:

- Sustained intensification was more likely with maximizing dose as compared to adding a new medication at three months (65% vs. 50%, respectively; average treatment effect (ATE) –15 percentage points; 95% CI, –16 to –15 percentage points; NNH=6).
  - Results were similar at 12 months.
- At three months, adding a new medication was associated with change in SBP of –4.6 mmHg versus –3.8 mmHg for maximizing dose, corresponding to an ATE of –0.8 mmHg (95% CI, –1.2 to –0.4 mmHg).
- At 12 months, the change in SBP was –5.6 mmHg for adding a new medication and –4.5 mmHg for maximizing dose, corresponding to an ATE of –1.1 mmHg (95% CI, –1.6 to –0.6 mmHg).

LIMITATIONS:

- The study was unable to determine why a person stopped taking medication.
- The data was susceptible to unmeasured confounding factors.
- It was uncertain as to why treatment was modified and why a specific intensification approach was used.
- Generalizability to individuals who identify as female was uncertain given population sampled.

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