GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT:
Effective Treatment of Acute MSK Low Back Pain

Effective Treatment of Acute MSK Low Back Pain

Topical Diclofenac Versus Oral Ibuprofen Versus Diclofenac + Ibuprofen for Emergency Department Patients with Acute Low Back Pain: A Randomized Study

Khankhel N, Friedman BW, Baer J, et al. Topical Diclofenac Versus Oral Ibuprofen Versus Diclofenac + Ibuprofen for Emergency Department Patients With Acute Low Back Pain: A Randomized Study. *Ann Emerg Med.* 2024;83(6):542-551. doi:10.1016/j.annemergmed.2024.01.037

KEY TAKEAWAY: Oral ibuprofen is likely more effective than topical diclofenac for the treatment of musculoskeletal (MSK) low back pain. Topical diclofenac has no significant additive benefit when used in combination with oral ibuprofen.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The lifetime prevalence of low back pain in the United States is over 80%. Previous studies support the use of non-steroidal anti-inflammatory drugs (NSAIDs) as first-line for the treatment of acute low back pain without sciatica compared to placebo. Topical NSAIDs are more effective than placebo for improving pain in patients with musculoskeletal sports injuries. However, there is limited high-quality research on the use of topical NSAIDs for the treatment of low back pain. This study sought to evaluate the effectiveness of topical diclofenac compared to oral NSAIDs and whether adding diclofenac to oral NSAIDs will provide additive improvement to pain management.

PATIENTS: Emergency department (ED) patients with low back pain

INTERVENTION: Diclofenac + placebo and diclofenac + ibuprofen

CONTROL: Ibuprofen + placebo

PRIMARY OUTCOME: Functional outcome at two days

Secondary Outcome: Functional outcome at seven days

METHODS (BRIEF DESCRIPTION):

- The study was conducted at two emergency departments affiliated with Montefiore Medical Center.
- Participants included patients 18–69 years old with acute musculoskeletal low back pain.
- Included patients with functionally impairing low back pain with a minimum score of five on the Roland Morris Disability Questionnaire (RMDQ); a 24-item questionnaire. Scores range from 0–24 with higher scores indicating increased physical impairment.
- The study excluded patients with radicular pain, pain lasting more than two weeks, pregnant patients, patients with open low back wounds, or patients on daily pain medications before the onset of their acute low back pain.
- Patients were randomized 1:1:1 to a two-day supply of either:
  - 1% diclofenac topical gel + oral placebo
  - 400 mg ibuprofen + 1% diclofenac topical gel
  - 400 mg oral ibuprofen + placebo topical gel
- Patients were given a 10-minute educational intervention before ED discharge.
- The change in RMDQ score between baseline ED visit and two-day follow-up was measured as the primary outcome.
- Changes in RMDQ score between baseline ED visit and seven-day follow-up were measured as the secondary outcome.
- A minimum of five-point improvement in RMDQ score was considered clinically significant.

INTERVENTION (# IN THE GROUP):

- Diclofenac + placebo: 66
- Diclofenac + ibuprofen: 65

COMPARISON (# IN THE GROUP): 66

FOLLOW-UP PERIOD: Two and seven days after ED discharge

RESULTS:

Primary Outcome –

- Diclofenac + placebo improved low back pain at day two compared to baseline (mean difference [MD] 6.4 points; 95% CI, 4.0–8.8).
- Diclofenac + ibuprofen improved low back pain at day two compared to baseline (MD 8.7 points; 95% CI, 6.3–11).
- Ibuprofen + placebo improved low back pain at day two compared to baseline (MD 10 points; 95% CI, 7.5–13).

- Ibuprofen improved low back pain at day two compared to diclofenac (between group MD 3.7; 95% CI, 0.2–7.2).
- There was no statistically significant change in low back pain at day two for the following:
  - Ibuprofen vs both (between group MD 1.4; 95% CI, –2.0 to 4.9)
  - Diclofenac vs both (between group MD –2.3; 95% CI, –5.7 to 1.0)

Secondary Outcome –

- Diclofenac + placebo improved low back pain at day seven compared to baseline (MD 9.5 points; 95% CI, 7.1–12).
- Diclofenac + ibuprofen improved low back pain at day seven compared to baseline (MD 11 points; 95% CI, 8.4–13).
- Ibuprofen + placebo improved low back pain at day seven compared to baseline (MD 12 points; 95% CI, 9.8–15).
- There was no statistically significant change in low back pain at day 7 for the following:
  - Ibuprofen vs diclofenac (between group MD 2.7; 95% CI, –0.7 to 6.1)
  - Ibuprofen vs both (between group MD 1.6; 95% CI, –1.8 to 4.9)
  - Diclofenac vs both (between group MD –1.2; 95% CI, –4.5 to 2.2)

LIMITATIONS:

- Participants' demographics are not a true representation of the US population as the majority were either Hispanic/Latino or Black/African American.
- The study reports being unable to mask the distinct smell of diclofenac which may affect the blinding of patients.
- The use of a four-point ordinal scale could be subjective.
- A seven-day post-ED visit RMDQ outcome was measured with only two days of treatment post-ED visit
- The RMDQ scale with a five-point change as the required minimum for clinically significant has not been validated in an ED setting.

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Can Individualized Homeopathic Medicines Put a Pause on Menopausal Syndrome?

Efficacy of Individualized Homeopathic Medicines in the Treatment of Menopausal Syndrome: Double-Blind, Randomized, Placebo-Controlled Trial

Ghosh S, Palanisamy C, Das AD, et al. Efficacy of Individualized Homeopathic Medicines in the Treatment of Menopausal Syndrome: Double-Blind, Randomized, Placebo-Controlled Trial. *J Integr Complement Med.* 2023;29(10):649-664. doi:10.1089/jicm.2022.0760

KEY TAKEAWAY: There is no clearly demonstrable difference in individualized homeopathic medicines for the treatment of menopausal syndrome compared to placebo.

STUDY DESIGN: Single site double-blind, randomized, placebo-controlled

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Menopause is the cessation of menstruation for at least a full year and is often associated with a variety of symptoms that negatively impact the quality of life in women 45–55 years old. The first-line treatment of hormone replacement therapy (HRT) is generally quite safe but does increase the risk of other pathologies and is also contraindicated in certain populations. Individualized homeopathic medicines (IHM) have shown several anecdotal incidences of success, however, there is still limited convincing evidence of IHMs in the treatment of menopausal syndrome compared to placebos.

PATIENTS: Women with menopausal syndrome

INTERVENTION: IHM + concomitant care

CONTROL: Placebo + concomitant care

PRIMARY OUTCOME: Menopausal symptoms

Secondary Outcome: Quality of life

METHODS (BRIEF DESCRIPTION):

- The study was done in the outpatient departments of Mahesh Bhattacharyya Homeopathic Medical College and Hospital (MBHMC&H), West Bengal, India on 60 women with menopausal syndrome.
- Women 40–55 years old with at least three months of menopausal symptoms and the ability to read and write English and Bengali were included in the study.
- Exclusion criteria:
  - Females on HRT because of artificial menopause
  - History of breast or gynecologic cancers
  - Active neurologic or psychiatric illnesses affecting the quality of life
  - Self-reported immune-compromised state
  - Undergoing homeopathic treatment for any other chronic conditions within the past three months
- Participants were blindly assigned IHM vs placebo in a 30:30 ratio
- The IHM group received 21 different homeopathic medications at baseline (Sulfur, Sepia, succus, Natrum muriaticum, and Pulsatilla nigricans accounting for 53%) prescribed according to homeopathic principles, with each dose consisting of 6–8 medicated globules of cane sugar.
- The placebo group received 6–8 non-medicated globules of cane sugar moistened with rectified spirit.
- Participants were all instructed to take medications orally on an empty stomach daily and encouraged to take a diet rich in phytoestrogens (walnuts, fruits, grains, and vegetables).
- Results were measured at baseline and then over three months in one-month intervals.
- The primary outcome was measured using the Greene Climacteric Scale (GCS) and the Menopause Rating Scale (MRS).
  - The GCS consists of 21 symptoms forming psychological, physical, vasomotor, and sexual subscales. Scores range from 0–63, with zero being not at all and four being extremely.
  - The MRS consists of 11 items of complaints, with each item scoring from 0-4 points, with zero being no complaints and four severe symptoms.
- The secondary outcome was measured using the Utian Quality of Life (UQOL), consisting of a 23-item validated instrument having four components including occupational, health, emotional, and sexual. Scores range from 1–4 points, with one being not true, and four being very true.

- Group differences were measured using two-way repeated measures of analysis of variance (ANOVA) models with $p<.025$ to be considered statistically significant for primary outcomes and $p<.05$ for secondary outcomes.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 30

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- There was no significant difference in menopausal symptom improvement between IHM users and placebo.
  - GCS total score difference ($F_{1,58}$ 1.4; $p=.25$)
  - MRS total score total score difference ($F_{1,56}$ 0.72; $p=.4$)

Secondary Outcome –

- There was also no significant difference in the quality of life between IHM users and placebo ($F_{1,58}$ 2.9; $p=.094$).

LIMITATIONS:

- Limited amount of participants.
- No standardization in the specific IHMs that were prescribed to each patient.
- Phytoestrogen dietary supplementation to both groups might have affected detecting differences in groups.
- Short follow-up time period

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Do Mind-Body Medicine Practices Reduce Blood Pressure?

Effect of Meditation, Mindfulness-Based Stress Reduction, and Relaxation Techniques as Mind-Body Medicine Practices to Reduce Blood Pressure in Cardiac Patients: A Systematic Review and Meta-Analysis

Wankhar D, Prabu Kumar A, Vijayakumar V, et al. Effect of Meditation, Mindfulness-Based Stress Reduction, and Relaxation Techniques as Mind-Body Medicine Practices to Reduce Blood Pressure in Cardiac Patients: A Systematic Review and Meta-Analysis. *Cureus.* 2024;16(4):e58434. Published 2024 Apr 17. doi:10.7759/cureus.58434

KEY TAKEAWAY: Mind-body medicine (MBM) practices do not result in a clinically significant reduction in systolic blood pressure and do not reduce diastolic blood pressure.

STUDY DESIGN: Systematic review and meta-analysis of 15 randomized control trials (RCTs) (N=927)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Elevated blood pressure is one of the major risk factors for the development of hypertension and cardiovascular disease. Individuals with stress, anxiety, and depression are more prone to develop hypertension. This study was designed to determine how MBM practices affect blood pressure control in patients with cardiovascular disease.

PATIENTS: Adults with diagnosed cardiovascular disease

INTERVENTION: Mind-body medicine

CONTROL: Active interventions

PRIMARY OUTCOME: Systolic blood pressure (SBP) and diastolic blood pressure (DBP)

METHODS (BRIEF DESCRIPTION):

- Only RCTs focusing on MBM interventions between 2000–2020 were included.
- 927 adult participants were enrolled, including men and women, with diagnoses of cardiovascular disease such as hypertension, heart failure, myocardial infarction, and coronary artery disease.
- Studies varied in their use of MBM techniques including mindfulness techniques, relaxation techniques, meditation techniques, and mindfulness-based stress reduction.
- Control groups in the studies were provided with various interventions such as health education, social programs, a waiting list, and routine care with or without drugs.
- Outcomes were measured by comparing SBP and DBP measurements between the intervention and control groups.
- A clinically significant decrease in blood pressure is generally defined as a reduction of at least 5–10 mmHg in SBP or 3–5 mmHg in DBP, but this was not clearly stated in the study.

INTERVENTION (# IN THE GROUP): 476

COMPARISON (# IN THE GROUP): 451

FOLLOW-UP PERIOD: 4–16 weeks

RESULTS:

Primary Outcome –

- MBM resulted in a statistically significant, but not clinically significant, lowering of SBP when compared to control (15 RCTs, N=927; standardized mean difference [SMD] –0.78; 95% CI, –1.4 to –0.20; I^2=94%).
- MBM did not reduce DBP compared to control (15 RCTs, N=927; SMD –0.26; 95% CI, –0.91 to 0.39; I^2=95%).

LIMITATIONS:

- There was significant heterogeneity observed among the studies using the I^2 test.

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The Testosterone Paradox: Can It Help or Hurt Your Heart?

Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism: A Real-Life Observational Registry Study Setting Comparing Treated and Untreated (Control) Groups

Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism: A Real-Life Observational Registry Study Setting Comparing Treated and Untreated (Control) Groups. *J Cardiovasc Pharmacol Ther.* 2017;22(5):414-433. doi:10.1177/1074248417691136

KEY TAKEAWAY: Testosterone (T) replacement in men with hypogonadism reduces overall mortality, cardiovascular mortality, risk of nonfatal strokes, and the risk of nonfatal myocardial infarctions.

STUDY DESIGN: Prospective, observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There are reports of increased cardiovascular (CV) risk and mortality in patients with testosterone deficiency (TD) who have received long-term therapy with testosterone replacement therapy (TRT). However, recent studies have demonstrated that TRT improves CV risk by improving lipid profiles, blood pressure, and hyperglycemia, and alleviating risk factors for metabolic syndrome in patients with TD. This study aimed to determine the risks and benefits of TRT in hypogonadal men.

PATIENTS: Hypogonadal men

INTERVENTION: TRT

CONTROL: No TRT

PRIMARY OUTCOME: Mortality (CV and non-CV), nonfatal myocardial infarction (MI), and stroke
Secondary Outcome: Glycemic control, lipid profile, blood pressure, liver function, testosterone levels

METHODS (BRIEF DESCRIPTION):

- This was a cumulative registry study that included 656 adult men with a mean age of 61±7.2 years old at the start with total T levels ≤12 nmol/L and symptoms of hypogonadism.
- Patients received TRT with parental T undecanoate (TU) 1,000 mg for 12 weeks following an initial six-week interval for up to 10 years.
- Men who did not receive TRT served as controls.
- Total plasma T levels, weight, waist circumference, BMI, hemoglobin, hematocrit, fasting glucose levels, HbA1c, systolic blood pressure (BP), diastolic BP, heart rate (HR), pulse pressure, rate pressure, lipid profile, C-reactive protein, and liver transaminases were measured at least twice a year for eight years.
- Prostate volume and prostate-specific antigen (PSA) were measured via specific questionnaires.

INTERVENTION (# IN THE GROUP): 360

COMPARISON (# IN THE GROUP): 296

FOLLOW-UP PERIOD: Eight years

RESULTS:

Primary Outcome –

- TRT reduced mortality compared to no TRT use (estimated between-group difference 0.08; 95% CI, 0.019–0.34).
  - The estimated reduction in mortality in the treatment group was 66%–92%.
- TRT reduced cardiovascular (CV) mortality.
  - 19 deaths were attributed to CV disease in the control group and two deaths occurred in the TRT group, but they were not attributable to CV disease.
- TRT reduced the risk of nonfatal stroke.
  - 30 nonfatal strokes occurred in the control group and zero in the TRT group.
- TRT reduced the risk of nonfatal MI.
  - 26 nonfatal MIs occurred in the control group and zero in the TRT group.

Secondary Outcome –

- TRT improved glycemic control:
  - Fasting glucose (adjusted difference [AD] –0.4 mmol/L; p<.0001)
  - HbA1c (AD –1.8%; p<.0001)
- TRT improved lipid profiles:
  - Total cholesterol (AD –2.6 mmol/L; p<.0001)
  - High-density lipoprotein (HDL) cholesterol (AD 0.5 mmol/L; p<.0001)
  - Low-density lipoprotein (LDL) cholesterol (AD –1.8 mmol/L; p<.0001)

    - Triglycerides (TGL) (AD –1.1 mmol/L; *p*<.0001)
    - Total cholesterol HDL ratio (AD –3.8 mmol/L; *p*<.0001)
    - Non-HDL cholesterol (AD –3.8 mmol/L; *p*<.0001)
- TRT improved BP parameters:
    - Systolic BP (AD –24 mmHg; *p*<.0001)
    - Diastolic BP (AD –16 mmHg; *p*<.0001)
    - HR (AD –6.3 bpm; *p*<.0001)
    - Pulse pressure (AD –8.1 mmHg; *p*<.0001)
    - Rate pressure product (AD –2,654; *p*<.0001)
- TRT improved liver enzyme function:
    - AST (AD –27 U/L; *p*<.0001)
    - ALT (AD –31 U/L; *p*<.0001)
- TRT use increased testosterone levels (AD 7.0 mmol/L; *p*<.0001).

LIMITATIONS:

- The patients were not randomized.
- Concomitant medications improving metabolic risk were not monitored.
- Patients with Klinefelter syndrome, other primary hypogonadism, and inflammatory bowel disease were placed in the TRT group by default and were younger resulting in age bias.
- Patients may have decided against TRT for financial reasons because it was unaffordable resulting in selection bias based on socioeconomic status.
- Statistics regarding prostate cancer were not documented.

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Is Eating Processed Food Associated with Mental Illness?

The Association of Ultra-Processed Food Consumption with Adult Mental Health Disorders: A Systematic Review and Dose-Response Meta-Analysis of 260,385 Participants

Mazloomi SN, Talebi S, Mehrabani S, et al. The association of ultra-processed food consumption with adult mental health disorders: a systematic review and dose-response meta-analysis of 260,385 participants. *Nutr Neurosci.* 2023;26(10):913-931. doi:10.1080/1028415X.2022.2110188

KEY TAKEAWAY: Eating processed food is associated with an increased risk of depression but not anxiety.

STUDY DESIGN: Meta-analysis of 14 cross-sectional studies, two case-control studies, and 10 cohort studies (N=260,385).

LEVEL OF EVIDENCE: STEP 3 (downgraded for low-quality evidence among anxiety studies)

BRIEF BACKGROUND INFORMATION: Ultra-processed foods have become a staple for many American diets due to their convenience and price. While studies have been completed on the association between mental health and processed foods, no studies have been concluded with great power or evidence. This is a concern for primary care because the prevalence of mental health disorders is increasing. This study aimed to see if there is an association between eating processed foods and mental illnesses of depression and anxiety.

PATIENTS: Healthy adults

INTERVENTION: Eating ultra-processed food

CONTROL: Avoiding ultra-processed food

PRIMARY OUTCOME: Risk of depression and anxiety

Secondary Outcome: Correlation of proportion of processed food in participants' diet and the risk of depression

METHODS (BRIEF DESCRIPTION):

- The bias of included studies was assessed with the Newcastle-Ottawa scale 26 studies were high quality and two were medium quality.
- Healthy adults >18 years old with no HIV/AIDS or pregnancy were included in the study.
- The diets were assessed with methods of food frequency, questionnaires, brief self-administered questionnaires, and 24-hour recalls.
- The meta-analysis did not describe how the comparison group was determined.
- A variety of questionnaires were used to determine if the participants had depression or anxiety.
- The derSimonian-laid weighted random-effects model was used to calculate effect estimates.
- Cochran Q and I-squared statistics were used to assess the heterogeneity of the studies.
- Subgroup analysis was done to assess other possible outcome effects such as study design, classification of food, diet assessment method, etc.
- Dose-response meta-analysis was done to calculate the relative risk for each 10% increase in processed food consumption.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 5–10 years

RESULTS:

Primary Outcome –

- Eating processed food was associated with a higher risk of depression when compared to not eating processed foods (24 studies, n=257,205; relative risk [RR] 1.3; 95% CI, 1.2–1.4; I^2=62%).
- Eating processed food was not associated with a higher risk of anxiety when compared to not eating processed foods (5 studies, n=10,307; RR 1.4; 95% CI, 0.86–2.1; I^2=78%).

Secondary Outcome –

- There was an 11% higher risk of depression for every 10% of caloric intake that was ultra-processed foods among adults (3 studies, n=49,331; RR 1.1; 95% CI, 1.0–1.2; I^2=89%).
- A positive linear association was seen between the amount of processed food eaten and the risk of depression (3 studies, n=49,331; p-nonlinearity=0.82, p-dose-response p<.001).

LIMITATIONS:

- Cross-sectional analyses were used in some studies and thus a causal relationship between mental health and consumption of processed foods cannot be stated.
- Poor diet quality may result from the mental health disorder itself instead of being a causative factor.

- It should be considered that poor diet may be a symptom of depression and not the cause of depression.
- External factors such as exercise, education, and socioeconomic factors were not considered.
- The study could not perform a meta-analysis on stress due to the lack of available research (one study found).
- Studies included were predominantly conducted before COVID-19. COVID-19 has had major impacts on mental health and consumption of processed foods and these associations should be studied further.
- The potential of recall bias could have under or overestimated the percentage of processed food consumption in participants' diets.

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CRISPR-Cas9 Editing for Treatment of Sickle Cell Disease

CRISPR-Cas9 Editing of the HBG1 and HBG2 Promoters to Treat Sickle Cell Disease

Sharma A, Boelens JJ, Cancio M, et al. CRISPR-Cas9 Editing of the HBG1 and HBG2 Promoters to Treat Sickle Cell Disease. *N Engl J Med.* 2023;389(9):820-832. doi:10.1056/NEJMoa2215643

KEY TAKEAWAY: Infusion of OTQ923 (CD34+ cells with edited genes) may increase the fraction of fetal hemoglobin staining in red cells (F cells) and fetal hemoglobin (fetal hemoglobin as a percentage of total hemoglobin) in patients with sickle cell disease as well as decrease the occurrence of vaso-occlusive crisis.

STUDY DESIGN: Phase 1/2 single-site trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding of participants and providers)

BRIEF BACKGROUND INFORMATION: Induction of fetal hemoglobin is a proven strategy for treating sickle cell disease. In patients with conditions where they produce more fetal cells, the symptoms of sickle cell disease are lessened. This study investigates the use of clustered regularly interspaced short palindromic repeats (CRISPR) to alter CD34 gene expression and increase F cells and fetal hemoglobin (Hgb) in hopes of reducing symptom burden in sickle cell patients.

PATIENTS: Adults with sickle cell disease

INTERVENTION: Gene editing with CRISPR

CONTROL: Baseline

PRIMARY OUTCOME: F cell and fetal hemoglobin at 6 and 18 months

Secondary Outcome: Clinical manifestation of sickle cell disease

METHODS (BRIEF DESCRIPTION):

- Patients 18–40 years old with sickle cell disease were infused with OTQ923 (hematopoietic cells with CRISPR-Cas9 editing) which induces fetal hemoglobin.
- Selected patients had three episodes of vaso-occlusive crisis or two episodes of chest syndrome in the last 24 months.
- Patients with a history of significant bleeding disorder or those currently pregnant/ lactating were excluded.
- The mean age was 22 years old with one woman and two males with baseline sickle cell disease genotype, two participants were previously treated with multiple blood transfusions, and all participants were previously treated with hydroxyurea.
- The study participants received monthly red cell exchange transfusions for at least two months before collection of CD34+ cells, which were then enriched and electroporated with the CRISPR-Cas9-gRNA-68 ribonucleoprotein complex to produce OTQ923.
- Participants underwent conditioning with myeloablative busulfan before infusion of the OTQ923.
- The primary outcome was the assessment of fetal hemoglobin expression (the percentage of fetal hemoglobin compared to total hemoglobin) and F cells (percentage compared to total red cells).
- The secondary outcome was shown to be a clinically significant reduction in sickle cell disease-related events (vaso-occlusive crises) measured by researchers at routine follow-ups starting one day after infusion of OTQ923 until the last follow-up.

INTERVENTION (# IN THE GROUP): 3

COMPARISON (# IN THE GROUP): The same 3 patients

FOLLOW-UP PERIOD: 18 months post-treatment

RESULTS:

Primary Outcome –

- All participants demonstrated an increase in F Cells and Fetal Hgb after OTQ923 infusion.
- Participant 1: Pretransfusion 4% F cells increased to 78% and 88% at 12 and 18 months, respectively.
  - Pretransfusion 0.4% fetal Hgb and increase post-transfusion to 25% and 27% at 12 and 18 months, respectively.
- Participant 2: Pretransfusion 20% F cells increased to 80% and 87% at six and 12 months, respectively.
  - Pretransfusion 4.2% fetal Hgb increased to 23% and 25% at six and 12 months, respectively.
- Participant 3: Pretransfusion 6.2% F cells increased to 70% and 86% at four and six months, respectively.
  - Pretransfusion 1.4% fetal Hgb increased to 19% and 23% at four and six months, respectively.

Secondary Outcome –

- All Participants only had one episode of vaso-occlusive crisis at 9–18 months after transfusion, which was a reduction in comparison to previous crises for all participants.

LIMITATIONS:

- This study had a limited sample size.
- The strict exclusion criteria limit generalizability.
- The toxicity of exposure to busulfan with the infusion would limit feasibility.
- The authors were affiliated with the funding of a drug development company (Novartis Pharmaceuticals).
- The study lacked extended follow-up, blinding for patients and comparison patients.

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Make Your Diabetes Therapy a Combo with a GLP-1 Receptor Agonist and SGLT-2 Inhibitor

Effect of Combination Treatment with Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter-2 Inhibitors on Incidence of Cardiovascular and Serious Renal Events: Population-Based Cohort Study

Simms-Williams N, Treves N, Yin H, et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study [published correction appears in BMJ. 2024 May 16;385:q1094. doi: 10.1136/bmj.q1094] [published correction appears in BMJ. 2024 Jun 5;385:q1237. doi: 10.1136/bmj.q1237]. *BMJ*. 2024;385:e078242. Published 2024 Apr 25. doi:10.1136/bmj-2023-078242

KEY TAKEAWAY: Combination therapy with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) is associated with a lower risk of major adverse cardiovascular events (MACE) and serious renal events compared with GLP-1 RAs alone in patients with type 2 diabetes (T2DM). Combination therapy is associated with a lower risk of MACE vs SLGT-2i therapy alone in patients with diabetes, but there was no impact on serious renal events.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: GLP-1 RAs and SGLT2is are frequently prescribed antihyperglycemic medications for managing T2DM. Individually, these drugs have demonstrated a reduction in the risk of cardiorenal events and mortality in extensive cardiovascular outcome trials. This study aimed to investigate the combined impact of these drug classes on these outcomes.

PATIENTS: Adults with T2DM

INTERVENTION: Combination therapy with GLP-1 RAs and SGLT-2is

CONTROL: GLP-1 RA or SGLT-2i

PRIMARY OUTCOME: Major adverse cardiovascular events and serious renal events

METHODS (BRIEF DESCRIPTION):

- Two new-user cohorts including adults ≥18 years old with T2DM were created from the UK Clinical Practice Research Datalink GOLD and Aurum databases.
- Exclusion criteria included patients with a history of GLP-1 RA or SGLT-2i having one year of medical history in the database, patients without diagnosis of T2DM before cohort entry, patients with end-stage renal disease, and patients with multiple endocrine neoplasia syndrome.
- The first cohort consisted of 6,696 patients receiving a GLP-1 RA (dulaglutide, exenatide, lixisenatide, semaglutide, and liraglutide except for 3 mg/0.5 mL weight loss formulation) prescription and subsequently added on an SLGT-2i prescription (canagliflozin, dapagliflozin, or empagliflozin) between January 1, 2013 and December 31, 2020.
- The second cohort consisted of 8,942 patients on an SLGT-2i who added a GLP-1 RA during this same time frame.
- In the cohort comparing combination therapy to those on GLP-1 RA alone, the mean age was 56 and 57 years old, respectively and the male sex made up 55% and 55%, respectively.
- In the cohort comparing combination therapy to those on SGLT-2i alone, the mean age was 58 and 57 years old, respectively, and the male sex made up 52% and 53%, respectively
- Using an on-treatment approach, new users were followed until treatment discontinuation, death, end of database registration, or end of study period (March 29, 2021).
- Patients on combination therapy (defined as prescriptions for both classes of medications within a 60-day grace period) with GLP-1 RA and SGLT-2i were compared to those on a GLP-1 RA or SGLT-2i alone.
- Outcomes were identified through inpatient diagnosis and mortality data within the database.
- Cohorts were matched for potential confounders.
- Major cardiovascular events included myocardial infarction, ischemic stroke, or cardiovascular mortality.
- Follow up was done in 30-day intervals.

INTERVENTION (# IN THE GROUP):

- Cohort 1: 6,696

- Cohort 2: 8,942

COMPARISON (# IN THE GROUP): Combination therapy was matched 1:1 with patients prescribed a GLP-1 RA or SGLT-2i (n=6,696 and n=8,942, respectively)

FOLLOW-UP PERIOD:

- GLP-1 RA cohort: median 9.0 months
- SGLT-2i cohort: median 8.4 months

RESULTS:

Primary Outcome –

- Combination therapy reduced major adverse cardiac events by 30% compared to the GLP-1 RA-only group (hazard ratio [HR] 0.70; 95% CI, 0.49–0.99).
- Combination therapy reduced serious renal events by 57% compared to the GLP-RA-only group (HR 0.43; 95% CI, 0.23–0.80).
- Combination therapy reduced major cardiac events by 29% compared to the SGLT-2i-only group (HR 0.71; 95% CI, 0.52–0.98).
- Combination therapy did not decrease serious renal events compared to the SGLT-2i-only group.

LIMITATIONS:

- The indication for initiating combination therapy for individual patients was not known.
- Race was not included as a demographic factor, reducing generalizability.
- Patient adherence is unknown.

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Ditch the Doctor's Office: Remote Blood Pressure Monitoring Works Just as Well

Remote Blood Pressure Monitoring with Social Support for Patients with Hypertension: A Randomized Clinical Trial

Mehta SJ, Volpp KG, Troxel AB, et al. Remote Blood Pressure Monitoring With Social Support for Patients With Hypertension: A Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(6):e2413515. Published 2024 Jun 3. doi:10.1001/jamanetworkopen.2024.13515

KEY TAKEAWAY: Remote blood pressure monitoring with or without additional social support performs similarly to traditional office visit management.

STUDY DESIGN: Randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and lack of double blinding)

BRIEF BACKGROUND INFORMATION: About 30% of US adults are diagnosed with hypertension (HTN), while only about half achieve appropriate blood pressure (BP) control, with worse outcomes in Black patients. Management of hypertension is traditionally performed in face-to-face office visits, which can be a barrier for some patients. This study investigated the effectiveness of traditional office visits for HTN management compared with HTN management via home blood pressure (BP) monitoring and text messaging check-ins, with or without additional social accountability, in a primarily Black study population.

PATIENTS: Black adults with an HTN diagnosis

INTERVENTION: Home BP monitoring with or without social support

CONTROL: Office-based management of HTN

PRIMARY OUTCOME: Systolic BP

Secondary Outcome: Diastolic BP, overall BP control (defined as normotension)

METHODS (BRIEF DESCRIPTION):

- Adults 18–75 years old with hypertension on anti-hypertension medication, with at least two elevated BP measurements in the prior two years (>150/90 mmHg or >140/90 mmHg for patients with diabetes or chronic kidney disease) were included in the study.
    - Participants were required to have a cell phone and identify a support partner.
- Patients with metastatic cancer, end-stage renal disease, congestive heart failure (CHF), dementia, or BMI >50 were excluded from the study.
- Included participants had a mean age of 60 years old, 71% female, 91% Black, 35% of patients had diabetes and 11% had chronic kidney disease (CKD).
- There were 3 study arms: Remote BP monitoring, remote BP monitoring with social support, and a control arm with traditional office-based management of HTN.
- Patients were randomly assigned to these arms in a 2:2:1 ratio.
    - Patients and research staff were not blinded to arm assignment, however investigators and data analysts were blinded.
- Remote BP monitoring arm: Patients received three text message prompts per week from study staff to submit their BP measurements. They also received one text message per week from study staff asking about their medication adherence.
- Remote BP monitoring with social support arm: Patients likewise received three text message prompts per week from study staff prompting them to submit BP measurements and one text message per week from study staff asking about their medication adherence. Patients in the social support arm self-selected a social support partner who received a text update on the patient once per week, then were able to opt in or out of study staff sending a feedback text to the patient on behalf of the support partner.
- Traditional office-based management of HTN: Patients' primary care providers (PCPs) were notified when their patient was enrolled. Subsequent BP medication management was then left to PCP.
- There were two trial phases in which the management of BP for the intervention arms differed:
    - Phase 1: Data for remote monitoring and medication adherence was sent to PCP via electronic health record (EHR) messaging, as a "nudge" for PCP to adjust medications. There were 151 patients in phase 1.

- Phase 2: A central team of nurses and a nurse practitioner were assigned to manage medication adjustments. There were 100 patients in phase 2.

INTERVENTION (# IN THE GROUP):

- Home monitoring: 100
- Home monitoring with social support: 97

COMPARISON (# IN THE GROUP): 49

FOLLOW-UP PERIOD: Four months

RESULTS:

Primary Outcome –

- Remote monitoring did not affect systolic BP compared to control at four months (adjusted mean difference [aMD] –5.3 mmHg; 95% CI, –11 to 0.15).
- Remote monitoring plus social support did not affect systolic BP compared to control at four months (aMD –0.91 mmHg; 95% CI, –6.4 to 4.6).

Secondary Outcome –

- Remote monitoring did not affect diastolic BP compared to control (aMD –1.9 mmHg; 95% CI, –5.1 to 1.3).
- Remote monitoring plus social support did not affect diastolic BP compared to control (aMD –0.63 mmHg; 95% CI, –3.8 to 2.5).
- Blood pressure control was achieved in 49% of patients in the remote monitoring arm, 31% of patients in the remote monitoring plus social support arm, and 40% of the control arm. There was no significant difference between the three groups.

LIMITATIONS:

- Small sample size in each group leads to lower power and a lack of precision in risk estimates.
- Participants and study staff were not blinded to the treatment group, which may have influenced outcomes.
- In phase 1, BP management was not standardized; PCPs received a message about a patient's BP control but changes in medication were not made systematically.
- There was no separate analysis of phase 1 vs phase 2 despite significant study design differences.

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