GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of February 27 - March 3, 2023

SPOTLIGHT: Can My DNA Help Treat My Depression?

Can My DNA Help Treat My Depression?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial

Oslin DW, Lynch KG, Shih M, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. *JAMA*. 2022; 328(2): 151–161.

KEY TAKEAWAY: Using pharmacogenomic testing to guide the selection of medical treatment for MDD reduces prescriptions of medications with predicted drug-gene interactions.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Choosing an antidepressant for treating major depressive disorder (MDD) is imprecise and achieves only a 30% remission rate from the original treatment option. This study investigates whether pharmacogenomic testing reduces predicted drug-gene interactions and whether the testing results in superior clinical outcomes for the remission of depression.

PATIENTS: Adults diagnosed with MDD

INTERVENTION: Pharmacogenomic test used to guide treatment

CONTROL: Usual antidepressant selection

PRIMARY OUTCOME: Drug-gene interaction risk, depression symptom remission

METHODS (BRIEF DESCRIPTION):

- Adults, 18 to 80 (mean 48) years old, at VA medical centers with Major Depressive Disorder who were either initiating or switching treatment with a single antidepressant were included.
- Exclusion criteria included active substance use disorder, bipolar illness, psychosis, borderline, or antisocial personality disorder.
- Baseline PHQ-9 was completed to confirm depression severity (total PHQ-9 score >9) as a part of the inclusion criteria.
- DNA was collected for pharmacogenomic testing, and patients were randomly assigned in a 1:1 ratio.
- In the pharmacogenomic-guided treatment group treatment was based on the results of the pharmacogenomic testing.
- The control group was treated as usual.
- Outcomes were assessed via repeat PHQ-9 scoring at four, eight, 12, 18, and 24 weeks.

INTERVENTION (# IN THE GROUP): 966

COMPARISON (# IN THE GROUP): 978

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- The pharmacogenomic-guided group was more likely to receive medication with a lower probability of drug-gene interaction compared to usual care (odds ratio [OR] 4.3; 95% CI, 3.5 to 5.4).
- The pharmacogenomic-guided group had higher remission rates before 24 weeks compared to usual care (OR 1.3; 95% CI, 1.1–1.6).
    - However, by 24 weeks the remission rates were not significantly different between the groups (OR 1.1; 95% CI, 0.84–1.5).

LIMITATIONS:

- 70% of the patients were males and 70% of patients were White; therefore, the study may not be generalizable to the general patient population.
- The "usual care" method/process was not identified in terms of an algorithm or sequence in antidepressant(s) selection.
- The pharmacogenomic-guided therapy is geared toward stopping "predicted" drug-gene interactions, so a level of uncertainty remains in terms of if a true interaction vs. merely a theoretical one is being prevented.

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Combining Acetazolamide with Loop Diuresis for Improved Decongestion in Decompensated Heart Failure

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N Engl J Med*. 2022;387(13):1185-1195. doi:10.1056/NEJMoa2203094

KEY TAKEAWAY: The use of acetazolamide along with loop diuretic therapy increases successful decongestion among patients with acute decompensated heart failure (ADHF).

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There have been low rates of successful decongestion of ADHF upon discharge using traditional intravenous diuresis; only 15–20% of discharged patients are shown to be free from clinical congestion. Prior research has suggested use of carbonic anhydrase inhibitors coupled with diuresis can improve fluid decongestion.

PATIENTS: Adults admitted to the hospital with ADHF

INTERVENTION: Acetazolamide coupled with loop diuresis

CONTROL: Loop diuresis alone

PRIMARY OUTCOME: Successful decongestion

Secondary Outcome: Death, duration of hospital stay

METHODS (BRIEF DESCRIPTION):

- Adult patients were recruited from 27 sites in Belgium. The mean age was 78 years old, 63% were male, and 99% were White.
- Inclusion criteria: Adults with chronic heart failure on comparable loop diuresis regimens admitted for ADHF with at least one clinical sign of volume overload (edema, pleural effusion, ascites) and an NT-proBNP level of more than 1,000 pg per mL, or BNP level of more than 250 pg per mL.
- Exclusion criteria were receipt of acetazolamide maintenance therapy or another proximal tubular diuretic including sodium-glucose cotransporter-2 (SGLT2) inhibitor, a systolic blood pressure less than 90 mmHg, and an estimated glomerular filtration rate (GFR) of less than 20 mL per min per 1.72 m^2 of body surface area.
- Patients were randomized in a 1:1 ratio to intervention and control:
  - Intervention: Loop diuresis PLUS IV bolus of acetazolamide (500 mg daily) during the next 2 days or until the occurrence of complete decongestion.
  - Control: Loop diuresis alone consisting of double their oral maintenance dose.
- Successful decongestion was defined as the absence of signs of volume overload calculated by the treating physician using a congestion score measuring. Higher scores indicate a worse condition.
  - Peripheral edema (0 to 4)
  - Pleural effusion (0 to 3)
  - Ascites (0 to 3).
- Scores were measured before administration of the treatment phase, at discharge, and during three months of follow-up.

INTERVENTION (# IN THE GROUP): 256

COMPARISON (# IN THE GROUP): 259

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- Within three days, acetazolamide with loop diuresis significantly improved successful decongestion compared to loop diuresis alone (42% vs 30%; risk ratio [RR] 1.5; 95% CI, 1.2–1.8).
- At the time of discharge, acetazolamide with loop diuresis significantly improved successful decongestion compared to loop diuresis alone (79% vs 63%; RR 1.3; 95% CI, 1.1–1.4).
- There was no significant difference in the doubling of serum creatinine, hypokalemia, or hypotension between the two groups.

Secondary Outcome –

- There was no significant difference in death or duration of hospital stay between the two groups.

LIMITATIONS:

- Nearly all participants were White, which limited the generalizability of the study to other racial or ethnic groups.

- Applicability was limited to recent heart failure patients, as the trial participants had chronic heart failure.

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Is Diet Soda Better than Standard Soda?

Association of Low- and No-Calorie Sweetened Beverages as a Replacement for Sugar-Sweetened Beverages with Body Weight and Cardiometabolic Risk: A Systematic Review and Meta-Analysis

McGlynn ND, Khan TA, Wang L, et al. Association of low- and no-calorie sweetened beverages as a replacement for sugar-sweetened beverages with body weight and cardiometabolic risk: A Systematic Review. *JAMA Network Open*. 2022;5(3). doi:10.1001/jamanetworkopen.2022.2092

KEY TAKEAWAY: Low- and no-calorie sweetened beverages (LNCSBs) are an appropriate substitute for sugar-sweetened beverages (SSBs) in adults who are overweight or obese and are at risk for or have diabetes.

STUDY DESIGN: Systematic review and meta-analysis of 17 randomized controlled trials (RCTs) (N=1,733)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to inconsistent outcomes)

BRIEF BACKGROUND INFORMATION: SSBs (e.g., sodas and juices) are one of the most significant sources of added sugar that are associated with weight gain and metabolic disorders (e.g., diabetes, hypertension, and hyperlipidemia). Most health organizations recommend water as a substitute for SSBs and also recommend against LNCSBs due to prior research indicating inconsistent findings regarding weight loss and cardiometabolic effects. LNCSBs are thought to alter taste receptors, endocrine signaling, and our gut microbiome. This review aims to determine if switching from SSBs to LNCSBs, from water to SSBs, and from LNCSBs to water can lead to decreased body weight and other cardiometabolic risk factors.

PATIENTS: Adults who are overweight or obese

INTERVENTION: LNCSBs or water

CONTROL: SSBs

PRIMARY OUTCOME: Body weight

Secondary Outcome: Cardiometabolic risk factors (BMI, body fat percentage, intrahepatocellular lipids, HbA1c, systolic blood pressure)

METHODS (BRIEF DESCRIPTION):

- RCTs were extracted from three databases: Medline, Embase, and the Cochrane Central Register of Controlled Trials from inception through 2021.
- 1,733 adults who were overweight or obese and who were at risk or had diabetes were included.
  - 12 trials (n=601) analyzed LNCSBs as a substitute for SSBs.
  - 3 trials (n=429) analyzed water as a substitute for SSBs.
  - 9 trials (N=974) analyzed LNCSBs as a substitute for water.
- The mean age of participants ranged from 22.9 to 47.8 years old, and female participants consisted of 30–100% of each study.
- Inclusion criteria: RCTs with at least two weeks of interventions comparing LNCSBs, SSBs, and/or water.
- Exclusion criteria: Trials with multimodal interventions, did not use other comparisons, children, or pregnant/breastfeeding females.
- Across the studies, the duration of the trials included ranged from 3 to 52 weeks with beverage dose included the following:
  - LNCSBs: 250–2,000 mL/d
  - Water: 250–2,000 mL/d
  - SSBs: 250–1,750 mL/d.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Median 12 weeks (3–52 weeks)

RESULTS:

Primary Outcome –

- LNCSBs as a substitute for SSBs significantly reduced body weight (12 RCTs, n=467; mean difference [MD] –1.1 kg; 95% CI, –1.7 to –0.41; GRADE certainty of evidence=moderate).
- Water as a substitute for SSBs didn't improve any outcomes.
- LNCSBs as a substitute for water didn't improve any outcomes.

Secondary Outcome –

- LNCSBs as a substitute for SSBs significantly:
  - Decreased BMI (9 RCTs, n= 437; MD -0.32; 95% CI, –0.58 to –0.07; GRADE certainty of evidence=low)

    - Decreased body fat percentage (7 RCTs, n= 210; MD –0.60%; 95% CI, –1.0% to –0.18%; GRADE certainty of evidence=moderate)
    - Decreased intrahepatocellular lipids (2 RCTs, n= 49; MD –0.42; 95% CI, –0.70 to –0.14; GRADE certainty of evidence=moderate)
- LNCSBs as a substitute for water significantly:
    - Increased HbA1c (4 RCTs, n=236; MD 0.21%; 95% CI, 0.02% to 0.40%; GRADE certainty of evidence=low)
    - Decreased systolic blood pressure (4 RCTs, n=425; MD –2.6 mmHg; 95% CI, –4.7 to –0.55; GRADE certainty of evidence=low).
- Water as a substitute for SSBs didn't improve any outcomes.

LIMITATIONS:

- Median follow-up duration of only 12 weeks did not allow for extrapolation of long-term outcomes.
- The outcomes were inconsistent (e.g., a decrease in BMI but no change in body weight).

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Could a Combined Prenatal Supplement Shorten Labor?

Peripartum Outcomes after Combined Myo-Inositol, Probiotics, and Micronutrient Supplementation from Preconception: The NiPPeR Randomized Controlled Trial

Chan SY, Yong HEJ, Chang HF, et al. Peripartum outcomes after combined myo-inositol, probiotics, and micronutrient supplementation from preconception: the NiPPeR randomized controlled trial [published online ahead of print, 2022 Aug 13]. *Am J Obstet Gynecol MFM*. 2022;4(6):100714. doi:10.1016/j.ajogmf.2022.100714

KEY TAKEAWAY: In healthy women, taking prenatal supplements with myo-inositol, micronutrients, and probiotics does not improve glycemic control compared to usual prenatal supplementation. However, these supplements result in a 20% shorter second stage of labor, less risk of operative delivery, and less blood loss.

STUDY DESIGN: Double-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Ingredients of prenatal supplements can widely vary, and little is known about the effect of various nutrients on peripartum outcomes. Research previously showed that prenatal supplements with myo-inositol, micronutrients, and probiotics reduced the risk of postpartum hemorrhage, but other effects are unknown.

PATIENTS: Healthy women desiring conception

INTERVENTION: Prenatal supplementation with specific nutrients and probiotics

CONTROL: Standard prenatal supplementation

PRIMARY OUTCOME: Glycemic control

Secondary Outcome: Peripartum labor events

METHODS (BRIEF DESCRIPTION):

- The study population included healthy women in the United Kingdom, Singapore, and New Zealand, 18 to 38 years old who desired conception between 2015 and 2017.
  - Participants were mostly White (61%) or Chinese (26%).
- 1,729 women were randomly assigned prenatal supplementation with myo-inositol, micronutrients (vitamin D, riboflavin, vitamin B6, vitamin B12, zinc), and probiotics (*lactobacillus rhamnosus* and *Bifido bacterium animalis ssp. Lactis*) or standard supplementation (folate, calcium, iron, iodine, and B-carotene) twice daily from preconception to delivery.
  - The study excluded women with medical conditions (diabetes, taking metformin, systemic steroids, anti-convulsive medication, hepatitis B, C, or HIV treatment), fetal loss, reproductive aids, or who were breastfeeding.
- Data were extracted from medical record review in urban hospitals and analyzed via multinomial (mutually exclusive), Poisson (categorical), and linear regression (continuous outcome) controlling for known covariates..

INTERVENTION (# IN THE GROUP): 293

COMPARISON (# IN THE GROUP): 290

FOLLOW-UP PERIOD: Through delivery

RESULTS:

Primary Outcome –

- Specific prenatal supplementation did not reduce the incidence of gestational diabetes compared to usual prenatal supplementation (adjusted risk ratio [aRR] 1.2; 95% CI, 0.92–1.6).

Secondary Outcome –

- Specific prenatal supplementation reduced the length of the second stage of labor by 20% compared to usual prenatal supplementation (adjusted mean difference [aMD] –12 minutes; 95% CI, –22 to –1.2).
- Specific prenatal supplementation reduced the risk of operative delivery in prolonged second-stage labor compared to usual prenatal supplementation (aRR 0.61; 95% CI, 0.40–0.93).
- Specific prenatal supplementation resulted in less blood loss compared to usual prenatal supplementation (aMD –35 mL; 95% CI, –70 to –3.5).
- Specific prenatal supplementation did not significantly affect labor induction, instrument-assisted vaginal delivery, operative delivery, post-partum hemorrhage, or the labor length of the first or third stages.

LIMITATIONS:

- Analysis of secondary outcomes instead of the primary outcomes increased the chance of statistical errors.

- The study population was not generalizable to women with medical conditions, ethnicities other than White and Chinese, or women in resource-poor areas.
- Recall bias in participants self-reporting their adherence to supplementation.
- Measurement bias in defining labor stages and estimating blood loss by obstetricians.
- Did not include fetal outcomes to assess for safety.

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Limited Benefit of Dual Bronchodilator Therapy for Tobacco-Exposed Patients without COPD

Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function

Han MK, Ye W, Wang D, et al. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022;387(13):1173-1184. doi:10.1056/NEJMoa2204752

KEY TAKEAWAY: Inhaled dual bronchodilator therapy does not result in significant improvement of respiratory symptoms compared to placebo in tobacco-exposed patients with preserved lung function on spirometry.

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Inhaled bronchodilator therapy is commonly used to treat respiratory symptoms, especially in patients with COPD. However, this therapy is also used to treat symptomatic tobacco-exposed patients who experience respiratory symptoms but do not meet COPD criteria, and few studies have been done to determine whether bronchodilator therapy is truly beneficial in this setting.

PATIENTS: Tobacco-exposed persons with COPD symptoms and preserved lung function on spirometry

INTERVENTION: Dual bronchodilator therapy

CONTROL: Placebo

PRIMARY OUTCOME: Symptoms measured with SGRQ
Secondary Outcome: Symptoms measured with additional scoring tools

METHODS (BRIEF DESCRIPTION):

- Tobacco-exposed people 40 to 80 years old with at least 10 pack-year histories scoring a 10 or higher on the COPD Assessment Test score, as well as FEV1:FVC ratio of ≥0.70 and FVC ≥70% on spirometry, indicating preserved lung function.
- Patients were blinded and randomized to one of the following treatments for 12 weeks:
  - Dual bronchodilator therapy: Indacaterol (27.5 mcg) plus glycopyrrolate (15.6 mcg)
  - Placebo
- Respiratory symptoms were measured using St. George's Respiratory Questionnaire (SGRQ), with a range from 1 to 100 (a higher score indicating worse symptoms).
  - The primary outcome for improvement was defined as a decrease of at least four points.
- Secondary outcomes predefined by:
  - A decrease by two in COPD Assessment Test (CAT) score (range from 0-40 with a higher score indicating worse symptoms).
  - A decrease by one in the Transitional Dyspnea Index (TDI) (range from –9 to 9 with a higher score indicating a greater decrease in the severity of dyspnea).
  - Combination of decrease of SGRQ score plus a TDI score of at least one.
- Symptoms were measured at baseline, 12 weeks, and four weeks after termination of the study over telephone to assess adverse events.

INTERVENTION (# IN THE GROUP): 227

COMPARISON (# IN THE GROUP): 244

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- There was no significant difference in symptoms between the placebo and treatment group (adjusted odds ratio [OR] 0.91; 95% CI, 0.60–1.4).

Secondary Outcome –

- There was no significant difference in symptoms between the placebo and treatment groups.
  - CAT score ≥2: OR 1.5 (95% CI, 0.96–2.2)
  - TDI score of ≥1: OR 1.1 (95% CI, 0.82–1.6)
  - Decrease of SGRQ score plus a TDI score of at least one: OR 0.97 (95% CI, 0.60–1.6)

LIMITATIONS:

- Symptoms could be due to other non-respiratory pathology.
- There may be a subgroup of patients who do benefit from treatment. Further studies are needed to determine if discontinuation of bronchodilator therapy would worsen conditions.
- The effect of glucocorticoids and non-bronchodilator COPD drugs was not studied.
- Long-term improvements cannot be assessed over 12 weeks.

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Keep It or Toss It? RAS Inhibition in Advanced CKD

Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease

Bhandari S, Mehta S, Khwaja A, et al. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *N Engl J Med*. 2022;387(22):2021-2032. doi:10.1056/NEJMoa2210639

KEY TAKEAWAY: There is no statistically significant difference in the long-term decrease of estimated glomerular filtration rate (eGFR) between patients with advanced and progressive Chronic Kidney Disease (CKD) on Renin-Angiotensin System (RAS), and those who discontinued these medications.

STUDY DESIGN: Multi-center, open-label, randomized controlled trial

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

BRIEF BACKGROUND INFORMATION: RAS inhibitors are medications that are used to slow the advance of CKD in its mild and moderate phases. There is currently no evidence that these medications are effective when CKD progresses to advanced stages. Some observational studies suggest that its discontinuation could increase eGFR in patients in these advanced stages.

PATIENTS: Adult patients with advanced and progressive CKD

INTERVENTION: Discontinuation of previously prescribed RAS inhibitors

CONTROL: Continuation of previously prescribed RAS inhibitors

PRIMARY OUTCOME: eGFR

Secondary Outcome: Progression of end-stage kidney disease (ESKD), initiation of renal replacement therapy, hospitalization, quality of life, exercise capacity, cardiovascular events, death

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from 39 healthcare centers in the United Kingdom.
- Eligibility included being over 18 years old, having stage 4 or 5 CKD with eGFR less than 30 mL/min per 1.73 m^2 of body surface area (BSA), and having been prescribed Angiotensin-Converting Enzyme (ACE) inhibitor, Angiotensin Receptor Blocker (ARB), or both for six months or longer.
- Exclusion criteria included current hemodialysis or status post kidney transplantation, uncontrolled hypertension, or history of stroke or myocardial infarction in the previous 3 months before the initiation of the study.
- Patients were randomly assigned to two groups, to either discontinue RAS inhibitors or continue these medications.
- Special precautions were taken to ensure that both groups were well represented for the following factors: age, initial eGFR, diabetes status, mean arterial pressure, and degree of proteinuria.
- The discontinuation group was permitted to use any antihypertensive medication except for ACE inhibitors and ARBs for blood pressure control.
- The continuation group was required to use these medications at therapeutic doses as determined by the clinician. They were permitted to have any other antihypertensive added per clinician judgment.
- The protocol-mandated target blood pressure was 140/85 mmHg or less.
- Progression to ESKD was determined by clinical criteria that included the implementation of terminal palliative care or renal replacement therapy.
- Hospitalization for any cause, cardiovascular events, and death were verified through access to hospital records during follow-up visits when these occurred.
- Exercise capacity was determined by the use of the six-minute walk test.
- Quality of life was measured by using the Kidney Disease Quality of Life 36-Item Short Form Survey, version 1.3.

INTERVENTION (# IN THE GROUP): 206

COMPARISON (# IN THE GROUP): 205

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- There was no difference in eGFR between the discontinuation and continuation groups (mean difference –0.7; 95% CI, –2.5 to 1.0).

Secondary Outcome –

- There was no difference in the progression of ESKD, initiation of renal replacement therapy, hospitalization, quality of life, exercise capacity, cardiovascular events, or death between the discontinuation and continuation groups.

LIMITATIONS:

- The patients were unable to be blinded due to the open-label nature of the study.
- The results are limited in generalizability due to the poor ethnic representation of participants.
- There was a relatively small number of participants.

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Midodrine Effective in Preventing Vasovagal Syncope Events in Healthy Adults

Midodrine for the Prevention of Vasovagal Syncope: A Randomized Clinical Trial

Robert Sheldon, Peter Faris, Anthony Tang, et al. Midodrine for the Prevention of Vasovagal Syncope: A Randomized Clinical Trial. *Ann Intern Med*. 2021; 174:1349-1356.

KEY TAKEAWAY: Midodrine is effective in limiting vasovagal syncope events.

STUDY DESIGN: Multi-site, multi-national, double-blind randomized control trial with 1:1 treatment-to-placebo ratio

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Vasovagal syncope has a high prevalence with no effective treatment options. Using Tilt testing, Midodrine is effective in preventing hypotension as well as syncope in this population.

PATIENTS: Individuals with recurrent vasovagal syncope episodes

INTERVENTION: Midodrine starting at 5 mg

CONTROL: Placebo

PRIMARY OUTCOME: Syncope

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Adults (median 32 years old) with Calgary Syncope Symptom Score of at least two and had experienced at least two episodes of syncope in the previous year.
- Exclusion Criteria: Any underlying cardiac disease, seizure disorder, liver disease, hypertension, orthostatic hypotension, or previous use of midodrine.
- Participants were randomized 1:1 to receive a placebo or midodrine.
    - Midodrine was initiated at a dose of 5 mg tid and adjusted as tolerated to doses from 2.5 mg twice daily up to 10 mg three times daily.
- Participants were not allowed the following treatments until after experiencing a syncopal episode: permanent pacemaker, b-blockers, all a1-adrenergic medications, tricyclic antidepressants, serotonin reuptake inhibitors, scopolamine, theophylline, or fludrocortisone.
- Reported syncopal episodes were verified by history and examination.

INTERVENTION (# IN THE GROUP): 67

COMPARISON (# IN THE GROUP): 66

FOLLOW-UP PERIOD: Every two months over one year

RESULTS:

Primary Outcome –

- Compared to placebo, patients taking midodrine experienced significantly fewer syncopal episodes (relative risk 0.69; 95% CI, 0.49–0.97).
- The time interval until the first recurrence of syncope was significantly longer in the midodrine group (hazard ratio 0.59; 95% CI, 0.37–0.96).

LIMITATIONS:

- Small sample size.
- Short duration.
- High population concentration at a single center.
- Some participants continued in the study despite not taking prescribed treatment.

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Short-Term Benefit of Hyaluronate Injections for Shoulder Tendinopathy Pain

Subacromial Injections of Low- or High-Molecular-Weight Hyaluronate Versus Physical Therapy for Shoulder Tendinopathy: A Randomized Triple-Blind Controlled Trial

Esmaily H, Mohebbi R, Rezasoltani Z, Kasaiyan S, Dadarkhah A, Mir M. Subacromial Injections of Low- or High-Molecular-Weight Hyaluronate Versus Physical Therapy for Shoulder Tendinopathy: A Randomized Triple-Blind Controlled Trial. *Clin J Sport Med*. 2022;32(5):441-450. doi:10.1097/JSM.0000000000000988

KEY TAKEAWAY: Hyaluronate (HA) injections are more effective than physical therapy (PT) in reducing pain in patients with shoulder tendinopathy.

STUDY DESIGN: Triple-blind randomized controlled trial with three parallel arms

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Shoulder pain is a very common and impairing problem. Physical therapy is an established treatment, but other nonsurgical modalities including but not limited to NSAIDs, corticosteroids, prolotherapy, botulinum toxin, and plasma-rich plasma have been commonly prescribed.

PATIENTS: Patients with shoulder tendinopathy

INTERVENTION: Subacromial injection with HA

CONTROL: PT

PRIMARY OUTCOME: Shoulder pain

Secondary Outcome: Shoulder range of motion (ROM), shoulder disability, quality of life (QoL)

METHODS (BRIEF DESCRIPTION):

- 79 patients 16–70 years old with shoulder tendinopathy, diagnosed by a combination of a physical exam, history, and MRI were randomly assigned to groups for high dose HA injection vs low dose HA injection vs PT alone.
- The intervention group received single dose injection of either high dose HA (>2,000 kDa Synogel) or low dose HA (500–700 kDa Hyalgan).
- The control group received 10 one hour long physical therapy sessions. Each session consisted of heat therapy, electric nerve stimulation, and stretching.
- Pain was measured with a visual analog scale (VAS) from 0 (no pain) to 100 (most pain) at baseline, one, three, and six months after interventions.
- Shoulder ROM was measured using a goniometer at baseline, one, and three months after interventions.
- Disability was measured using the DASH questionnaire which was converted to a 0-100 scale (higher score means more disabilities) at baseline one, and three months after interventions.
- Quality of life was evaluated on physical health, psychological health, level of independence, social relationships, and environment using WHOQOL-Bref questionnaire which was converted to a 0–100 scale (higher score means improved QOL) measured at baseline and three months after the intervention.

INTERVENTION (# IN THE GROUP):

- High dose: 27
- Low dose: 28

COMPARISON (# IN THE GROUP): 24

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- High dose HA injections reduced shoulder pain at rest compared to physical therapy at three months (3.2 vs 1.1; *P*=.001).
- Low dose HA injections reduced shoulder pain at rest compared to physical therapy at three months (3.0 vs 1.1; *P*=.001).
- However, there was no significant difference between the groups at six months.

Secondary Outcome –

- High dose HA injections improved physical health compared to physical therapy at three months (–29 vs –18; *P*=.002).
- Low dose HA injections improved physical health compared to physical therapy at three months (–29 vs –18; *P*=.002).
- High dose HA injections decrease shoulder disability compared to physical therapy at three months (35 vs 19; *P*<.001).
- Low dose HA injections decrease shoulder disability compared to physical therapy at three months (39 vs 19; *P*<.001).

LIMITATIONS:

- Small sample size.
- There was a possible placebo effect of injection, given the recurrence of pain in the HA groups after three months of treatment.
- A longer follow-up period could provide more valuable data regarding differences over time.

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Clinical Diagnosis of Vaginitis versus the Use of a Vaginal Panel Assay

Performance of a Vaginal Panel Assay Compared with the Clinical Diagnosis of Vaginitis

Broache M, Cammarata CL, Stonebraker E, et al. Performance of a Vaginal Panel Assay Compared with the Clinical Diagnosis of Vaginitis. *Obstetrics & Gynecology*. 2021;138(6):853-859. doi:10.1097/aog.0000000000004592

KEY TAKEAWAY: The vaginal panel assay provides significantly better diagnostic accuracy for vaginitis than clinical diagnosis.

STUDY DESIGN: Prospective cross-sectional diagnostic accuracy study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to gold standard reference not utilized)

BRIEF BACKGROUND INFORMATION: Vaginitis, most commonly caused by bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis, is a common reason for healthcare visits in the United States. Vaginitis has traditionally been diagnosed using medical history, clinical findings, and wet-mount microscopy, but nucleic acid amplification tests have shown better diagnostic accuracy.

PATIENTS: Patients with symptoms of vaginitis

INTERVENTION: Vaginal panel assay

CONTROL: Clinical diagnosis

PRIMARY OUTCOME: Agreement of clinical diagnosis vs vaginal panel assay for bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis

METHODS (BRIEF DESCRIPTION):

- Investigators included patients presenting to one of five women's health clinics with symptoms suggestive of vaginitis.
- Participants had an average age of 32.9 ±11.1 years and most were known to be HIV-negative (74.5%).
- Symptoms reported included abnormal vaginal discharge (70.8%), painful or frequent urination (18.9%), vaginal itching, burning, or irritation (56.5%), painful or uncomfortable intercourse (12.7%), and vaginal odor (49.5%).
- A vaginal panel assay was obtained utilizing a vaginal swab, collected by the health care provider or the patient.
- At the same visit, a vaginal swab was obtained and utilized for clinical diagnosis of vulvovaginal candidiasis, bacterial vaginosis, and trichomoniasis using wet mount microscopy and the description of vaginal discharge.
- Positive, negative, and overall percent agreement were calculated between clinical diagnosis and vaginal panel assay for all three vaginitis types being evaluated.

INTERVENTION (# IN THE GROUP): 469 specimens

COMPARISON (# IN THE GROUP): Participants had both diagnostic tests to assess accuracy

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The positive percentage agreement between clinical diagnosis and vaginal panel assay was:
  - 58% (95% CI, 52%–64%) for bacterial vaginosis
  - 54% (95% CI, 45%–62%) for vulvovaginal candidiasis
  - 28% (95% CI, 12%–49%) for trichomoniasis
- The negative percentage agreement was:
  - 80% (95% CI, 74%–85%) for bacterial vaginosis
  - 77% (95% CI, 72%–81%) for vulvovaginal candidiasis
  - 99.8% (95% CI, 98.7–99.9) for trichomoniasis
- The percentage of positive assay results not treated for vaginitis based on negative clinical diagnosis was:
  - 65% for bacterial vaginosis
  - 44% for vulvovaginal candidiasis
  - 56% for trichomoniasis

LIMITATIONS:

- This study was supported by a medical device company.
- The study may be underpowered as the authors did not meet the expected recruitment goal for participants with trichomonas infections.
- Demographics such as sexual practices and prior infection were not reported.
- The assay of interest was not compared to culture, the traditional gold standard.

- Return to care/follow-up visits were not reported for those with a negative clinical diagnosis but positive assay.

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