GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

Volume 4 - Issue 31

FPIN
Family Physicians Inquiries Network

## What's in this week's issue?

**Week of July 29 - August 2, 2024**

### SPOTLIGHT: Which Exercise Routines Help Lower Blood Pressure?

# What Exercise Routines Help Lower Blood Pressure?

**Exercise Training and Resting Blood Pressure: A Large-Scale Pairwise and Network Meta-Analysis of Randomized Controlled Trials**

Edwards JJ, Deenmamode AHP, Griffiths M, et al. Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomized controlled trials. *Br J Sports Med.* 2023;57(20):1317-1326. doi:10.1136/bjsports-2022-106503



**KEY TAKEAWAY:** Multiple different exercise training modes reduce resting blood pressure with the most significant decrease with isometric exercises.

**STUDY DESIGN:** Large-scale pairwise and network meta-analysis of 270 randomized controlled trials (RCTs) (N=15,827)

**LEVEL OF EVIDENCE:** STEP 1

**BRIEF BACKGROUND INFORMATION:** Exercise given to patients as a prescription to reduce blood pressure is a well-established, non-pharmacological intervention. However, current guidelines regarding these exercise programs are based on outdated data and do not include recent exercise modes such as high-intensity interval training or isometric exercise training. This systematic review looked at randomized control studies to better support the development of updated exercise guidelines for the non-pharmacological treatment of hypertension.

**PATIENTS:** Healthy adults

**INTERVENTION:** Various exercise modalities

**CONTROL:** No assigned exercise program

**PRIMARY OUTCOME:** Resting blood pressure

**METHODS (BRIEF DESCRIPTION):**

- All healthy adults without limitations on health or disease, including all genders, races, ethnicities, and socioeconomic levels, were included.
  - No numerical breakdown for patient demographics was provided.
- Five different exercise modalities were included:
  - Aerobic exercise including walking, running, and cycling
  - Dynamic resistance training
  - Combined training
  - High-intensity interval training was defined as "episodic short bouts of high-intensity exercise separated by short periods of recovery at a lower intensity"
    - Sprint interval: "All-out" maximal, low-volume protocol
    - Aerobic interval: 4x4 in protocols of a lower intensity
  - Isometric exercise training: 4x2 minute contractions separated by 1–4 minute rest interval three times per week
    - Isometric handgrip: 30% maximum voluntary contraction
    - Isometric leg extension: Performed at 95% of peak heart rate (HR) during a lab-based maximal incremental isometric exercise test
    - Isometric wall squat: Knee joint angle that would elicit a rate of perceived exertion (RPE) of 3.4–4.5/10 for one; 5–6/10 bout two, 6.5–7.5/10 bout three, 8–9/10 bout four.
- Based on the Society of Hypertension/European Society of Cardiology guidelines baseline blood pressures were categorized into normotension (<130/85), prehypertension (130–139/85–89), or hypertension (>140/90).
- Blood pressures were then compared through systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes using weighted mean difference and 95% confidence intervals.

**INTERVENTION (# IN THE GROUP):** 8,195

**COMPARISON (# IN THE GROUP):** 7,632

**FOLLOW-UP PERIOD:** At least two weeks

**RESULTS:**

Primary Outcome –

- The following exercise models improved SBP compared to no exercise:
  - Aerobic exercise training (weighted mean difference [wMD] 4.5; 95% CI, 3.5–5.5; $I^2$=92)
  - Dynamic resistance training (wMD 4.6; 95% CI, 3.2–5.9; $I^2$=58)
  - Combined training (wMD 6.0; 95% CI, 3.2–8.9; $I^2$=93)
  - Isometric exercise training (wMD 8.2; 95% CI, 6.5–10; $I^2$=69)

    - High-intensity interval training (wMD 4.1; 95% CI, 2.6–5.5; $I^2$=82)
        - However, in looking only at aerobic interval training, there was no improvement (wMD 2.0; 95% CI, –1.2 to 5.1; $I^2$=67).
- The following exercise models improved DBP compared to no exercise:
    - Aerobic exercise training (wMD 2.5; 95% CI, 1.8–3.2; $I^2$=92)
    - Dynamic resistance training (wMD 3.0; 95% CI, 2.2–3.9; $I^2$=67)
    - Combined training (wMD 2.5; 95% CI, 1.1–4.0; $I^2$=85)
    - Isometric exercise training (wMD 4.0; 95% CI, 2.7–5.3; $I^2$=64)
    - High-intensity interval training (wMD 2.5; 95% CI, 1.2–3.8; $I^2$=91)
        - However, in looking only at aerobic interval training, there was no improvement (wMD 2.6; 95% CI, –0.5 to 5.7; $I^2$=84)
- Based on SUCRA values isometric exercise training had an effectiveness of 90% for decreasing resting SBP and 89% effectiveness for decreasing resting DBP.

**LIMITATIONS:**

- The RCTs that were included in this systematic review had poor control group activity monitoring.
- Many of the RCTs that were included were missing intention-to-treat analyses.
- These studies were not blinded with participant and investigator awareness on group allocation leading to increased biases such as significant publication bias for overall aerobic exercise training and isometric exercise training.
- Overall, there are fewer RCTs for certain exercise modes such as sprint interval training, aerobic interval training, isometric leg extension, and isometric wall squat resulting in these not being stratified and analyzed by baseline blood pressure status which was available for other exercise modalities. This limits the strength of the results due to the unknown starting baselines for these groups which showed great potential in decreasing resting blood pressures.
- A majority of RCTs set a threshold for inclusion of >80% of sessions completed; this led to the training compliance moderator analysis that was performed not including low attendance rates. These findings then must be interpreted in the context of individuals who are compliant with treatment modalities.

***Melissa Saganich, DO***
*Cahaba Medical Care FMRP*
*Centreville, AL*

# Two Kiwis a Day to Keep Constipation Away?

**Consumption of 2 Green Kiwifruits Daily Improves Constipation and Abdominal Comfort- Results of an International Multicenter Randomized Controlled Trial**

Gearry R, Fukudo S, Barbara G, et al. Consumption of 2 Green Kiwifruits Daily Improves Constipation and Abdominal Comfort-Results of an International Multicenter Randomized Controlled Trial. *Am J Gastroenterol*. 2023;118(6):1058-1068. doi:10.14309/ajg.0000000000002124



**KEY TAKEAWAY:** Daily consumption of two green kiwifruits significantly increased complete spontaneous bowel movements (CSBM) and improved gastrointestinal (GI) symptoms in individuals with constipation.

**STUDY DESIGN:** Prospective, single-blind, crossover randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Functional gastrointestinal disorders (FGID) are a widespread condition affecting more than 10% of the global population and causing significant morbidity and societal costs. Despite their impact, only 22% seek medical care, and common treatments like laxatives face limited tolerance. Previous studies have shown that two green kiwifruits improve the number of weekly bowel movements; however, no large studies have examined the effect of kiwifruits on the number of bowel movements and their effect on gastrointestinal (GI) comfort.

**PATIENTS:** Adults 18–65 years old

**INTERVENTION:** Kiwifruits

**CONTROL:** Psyllium

**PRIMARY OUTCOME:** CSBM

Secondary Outcome: GI symptoms

**METHODS (BRIEF DESCRIPTION):**

- The study was a 16-week crossover trial conducted in three countries.
- Participant demographics:
  - 136 females, 48 males
  - BMI 18–35 kg/$m^2$
- Participants had constipation-predominant irritable bowel syndrome (IBS-C), functional constipation (FC), or were healthy control (HC)
  - FC=60, IBS-C=61, HC=63
- Subjects were excluded if they had severe IBS symptoms, GI alarm symptoms, significant GI disorders, surgery, or other significant chronic conditions, pregnant, or women who intended to become pregnant or were breastfeeding.
- Participants were randomized into an intervention arm of either daily treatment with:
  - 7.5 g psyllium
  - Two green Zespri kiwifruits (approximately 6 g of fiber) with the kiwi skin removed
- After a two-week lead-in period, participants completed their assigned intervention for four weeks. This was followed by a four-week washout period, and then they completed the other intervention arm for an additional four weeks.
- The number of CSBM was recorded in a daily diary.
  - The change in the number of CSBM between the baseline week and week four of the intervention was reported with a goal of >1.5 per week.
- GI symptoms were measured using the GI Symptom Rating Scale (GSRS):
  - 15 questions looking at five symptom groups: Reflux, abdominal pain, indigestion, diarrhea, and constipation; scored 1–7 with higher scores indicating more troublesome symptoms.
- Results were recorded as difference between the baseline week and final treatment week in each intervention arm.

**INTERVENTION (# IN THE GROUP):** 121

**COMPARISON (# IN THE GROUP):** The same 121 patients

**FOLLOW-UP PERIOD:** Four weeks

**RESULTS:**

Primary Outcome –

- Green kiwifruit resulted in >1.5 CSBMs per week compared to baseline in FC, IBS-C, and FC+IBS-C:
  - HC (mean difference [MD] 1.2; $p$=.0022)
  - FC (MD 1.5; $p$<.0001)
  - IBS-C (MD 1.7; $p$=.0003)
  - FC + IBS-C (MD 1.7; $p$<.0001)
- Psyllium resulted in >1.5 CSBMs per week for the IBS-C group only.
  - HC (MD 1.3; $p$=.0022)
  - FC (MD 0.67; $p$=.1125)
  - IBS-C (MD 1.9; $p$=.0051)

    - FC + IBS-C (MD 0.9; *p*=.0007)
- Green kiwifruit resulted in more CSBMs than psyllium in the FC+IBS-C group, and similar CSBMs in all other groups:
    - HC (*p*=.84)
    - FC (*p*=.062)
    - IBS-C (*p*=.39)
    - FC+IBS-C (*p*=.038)

Secondary Outcome –

- Green Kiwifruit consumption reduced GI symptoms (GSRS total) in the FC, IBS-C, and FC+IBS-C group compared to baseline:
    - FC (MD –0.66; *p*<.0001)
    - IBS-C (MD –0.8; *p*<.0001)
    - FC+IBS-C (MD –0.36; *p*<.0001)
- Psyllium consumption reduced GI symptoms (GSRS total) only in the IBS-C group compared to baseline
    - IBS-C (MD –0.69; *p*<.0001)

**LIMITATIONS:**

- The patient population was selected from three countries New Zealand, Italy, and Japan, populations with diets vastly different can limit the generalizability of the study.
- Underrepresentation of men in the study
- This was not a double-blinded study as participants were unable to be blinded to the different interventions.
- Short treatment duration of four weeks
- Subjective ratings for secondary outcomes
- Individual's diet was not controlled.

***Emma Vaudreuil, DO***
*Texas A&M FMR*
*Bryan, TX*

# Is Oral Ibrexafungerp an Effective Treatment for Acute Vulvovaginal Candidiasis?

**Efficacy and Safety of Oral Ibrexafungerp for the Treatment of Acute Vulvovaginal Candidiasis: A Global Phase 3, Randomized, Placebo-Controlled Superiority Study (VANISH 306)**

Sobel R, Nyirjesy P, Ghannoum MA, et al. Efficacy and safety of oral ibrexafungerp for the treatment of acute vulvovaginal candidiasis: a global phase 3, randomized, placebo-controlled superiority study (VANISH 306). *BJOG*. 2022;129(3):412-420. doi:10.1111/1471-0528.16972



**KEY TAKEAWAY:** Ibrexafungerp is more effective than a placebo for vulvovaginal candidiasis.

**STUDY DESIGN:** Randomized, placebo-controlled superiority study

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis worldwide and treatment has been largely limited to the azole class of fungistatic agents. Ibrexafungerp is a first-in-class drug that blocks the synthesis of the fungal cell wall. Ibrexafungerp has *in vitro* fungicidal activity against different *Candida* species strains, including those that are echinocandin- and azole-resistant.

**PATIENTS:** Female patients ≥12 years old with acute VVC

**INTERVENTION:** Ibrexafungerp (300 mg twice for 1 day)

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Clinical cure

Secondary Outcome: Adverse events

**METHODS (BRIEF DESCRIPTION):**

- 449 patients were included in the intention-to-treat population and randomly assigned to ≥1 dose of ibrexafungerp (*n*=298) or matching placebo (*n*=151).
  - There were 18 study sites in Bulgaria and 19 study sites in the USA.
- All patients had a positive culture for ≥1 *Candida* species at baseline, with most testing positive for *C. albicans.*
- Participants, investigators, and outcome assessors were masked and allocation was concealed.
- The groups were well-balanced after randomization.
- Patients monitored their symptoms via regular self-assessment and reporting.
- Outcomes were reported using the Vulvovaginal Symptom Scale (VSS) which is a rating scale where patients report the intensity and frequency of symptoms such as itching, burning, discharge, and pain.
  - This study evaluated severe VVC, defined as a VSS score ≥4 at baseline.
  - The VSS allows for standardized measurement of symptom severity, aiding in the evaluation of treatment effectiveness by providing quantifiable data on symptom improvement or resolution over time.

**INTERVENTION (# IN THE GROUP):** 188

**COMPARISON (# IN THE GROUP):** 84

**FOLLOW-UP PERIOD:** 30 days

**RESULTS:**

Primary Outcome –

- Compared to placebo, patients receiving ibrexafungerp had significantly higher rates of clinical cure (63% vs 44%, respectively; relative risk [RR] 1.4; 95% CI, 1.1–1.8; NNT=5) at the test-of-cure visit.

Secondary Outcome –

- Ibrexafungerp was generally well tolerated. Adverse events were primarily gastrointestinal and were mild to moderate in severity.

**LIMITATIONS:**

- This study was limited by a lack of racial/ethnic diversity and low numbers of patients with a body mass index >35.
- Though the study was open to patients ≥12 years old, no one <18 years old was enrolled.
- The study included only a small number of patients with non-*albicans* infections, thus limiting efficacy determinations in these non-*albicans* species.

***Karen Olorunfemi, MD***
*Lewisgale Medical Center FMRP*
*Roanoke, VA*

# Clinical Tools to Optimize Use of Drug Regimens for DM2 with Atherosclerotic Disease

**Coordinated Care to Optimize Cardiovascular Preventative Therapies in Type 2 Diabetes: A Randomized Clinical Trial**

Pagidipati NJ, Nelson AJ, Kaltenbach LA, et al. Coordinated Care to Optimize Cardiovascular Preventive Therapies in Type 2 Diabetes: A Randomized Clinical Trial. *JAMA*. 2023;329(15):1261-1270. doi:10.1001/jama.2023.2854



**KEY TAKEAWAY:** Deliberate care coordination increases the prescribing of evidence-based medications for cardiovascular health in patients with type 2 diabetes mellitus (DM2).

**STUDY DESIGN:** Cluster randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Triple medication therapy (which includes high-intensity statins, ACEIs or ARBs, and SGLT2 inhibitors or GLP-1s) is effective at reducing the risk of cardiovascular disease in patients with DM2. However, the percentage of patients taking all three groups of recommended medications is low (ranging 2.7–14%). Few studies have previously analyzed effective strategies to increase clinical adherence to the guidelines in prescribing the recommended regimen.

**PATIENTS:** Adults with both DM2 and atherosclerotic cardiovascular disease

**INTERVENTION:** A multifaceted intervention to coordinate care and assess barriers

**CONTROL:** Usual care

**PRIMARY OUTCOME:** Proportion of patients prescribed medication in all three recommended groups at the last follow-up visit.

Secondary Outcome: Blood pressure, A1C, LDL level

**METHODS (BRIEF DESCRIPTION):**

- Cardiology clinics were randomized to usual care or intervention. 1,049 participants enrolled, across the US including 459 patients at 20 intervention clinics and 590 patients at 23 usual care clinics.
- In the intervention group 71% were white, 17% black and 11% Hispanic. In the usual care group 81% were white, 16% black and 6.4% Hispanic. The median age was 70 years old. 32% of the study participants were women. 70% of each group were insured through Medicare.
- Patients in the study had DM2 with atherosclerotic cardiovascular disease.
- Those with GFR <30 or an absolute CI to any of the medications, statin-associated side effects, A1C <7 and taking metformin, and patients already taking GLP1 or SGLT2 inhibitors were excluded.
- The intervention team consisted of a cardiologist, an endocrinologist, and a care specialist who performed a six-part intervention containing analysis of barriers, addressing barriers, education to providers and participants, navigation of prior authorizations, and quality metrics.
- Barriers to prescribing were analyzed and addressed by involving pharmacies, problem-solving ways to aid in prior authorization, and finding resources to aid patients with costs.
- Coordination of care was implemented by using electronic medical record (EMR) template letters to other providers.
- Education was provided to providers, with monthly online conferences, and lectures on evidence supporting triple therapy.
- Quality metrics and patient tracking of use were applied, and the status of triple therapy medications was labeled as (prescribed, in discussion, or not prescribed).
- The patients enrolled in the intervention group were provided educational materials at the start of the study, to encourage compliance and adherence.
- A baseline composite medication score for ACE/ARB, statin, and metformin was used to give patients a score of zero, one, or two points for medications they were taking at baseline.
- Primary outcomes were measured by counting the number of patients prescribed all three groups of medications at the last follow-up visit (at 6 months or 12 months).
    - Adjustment for the baseline composite score was made during the analysis of the results.

**INTERVENTION (# IN THE GROUP):** 459

**COMPARISON (# IN THE GROUP):** 590

**FOLLOW-UP PERIOD:** 12 months

**RESULTS:**

Primary Outcome –

- The coordinated care intervention significantly increased the prescribing of all three evidence-based therapy medications compared to usual care (38% vs 15%, respectively; *P*<.001).

Secondary Outcome –

- The intervention resulted in no measurable difference between the two groups regarding cardiovascular risk factors including systolic blood pressure, diastolic blood pressure, LDL-C, or A1C.
- There was no difference in clinical events including death, hospitalization for MI, stroke, or decompensated heart failure between patients in the intervention group vs the control group (adjusted hazard ratio [aHR] 0.79; 95% CI, 0.46–1.3).
- There was no significant difference in mortality between patients in the coordinated care group and patients in the standard care group (mortality difference 1.3% vs 2.7%, respectively; aHR 0.62; 95% CI, 0.24–1.6).

**LIMITATIONS:**

- The COVID-19 pandemic limited the ability of the intervention team to visit the clinics in person, potentially reducing the impact of the intervention.
- The study sites were randomized as intervention vs usual care, before the recruitment of participants to the study which could have led to influence over patients selected.
- Although adjusted during the final statistical analysis, the groups had differing baseline medication use before starting the study.
- Patient demographics were similar in the intervention vs regular care groups however not representative of the general public.

***Brittany Gray, DO***
*Abrazo FMRP*
*Phoenix, AZ*

# Self-Management of Hypertension Using E-Health Technology

**Associations Between Daily Home Blood Pressure Measurements and Self-Reports of Lifestyle and Symptoms in Primary Care: The PERHIT Study**

Andersson U, Nilsson PM, Kjellgren K, Ekholm M, Midlöv P. Associations between daily home blood pressure measurements and self-reports of lifestyle and symptoms in primary care: the PERHIT study. *Scand J Prim Health Care.* Published online March 26, 2024. doi:10.1080/02813432.2024.2332745



**KEY TAKEAWAY:** The use of an interactive web-based self-management system increases the proportion of individuals who had a blood pressure (BP) lower than 140/90 after eight weeks, but not at 12 months.

**STUDY DESIGN:** Randomized control trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to lack of blinding, high risk of bias, and limited generalizability)

**BRIEF BACKGROUND INFORMATION:** Technology and communication devices can assist physicians' decisions to make medication adjustments. Patient education can improve medication adherence. Previous studies conclude that self-monitoring of BP is effective in lowering BP when combined with counseling or education. There has been concern that patients have elevated blood pressure in the doctor's office but not at home, termed white coat syndrome. This study aims to address the effect of a person-centered approach to blood pressure management using e-health technology by individuals being treated for hypertension and obtaining a BP goal of less than 140/90 mmHg.

**PATIENTS:** Hypertensive patients with uncontrolled blood pressure

**INTERVENTION:** E-health self-management system

**CONTROL:** Usual care

**PRIMARY OUTCOME:** Percentage of patients with BP less than 140/90 mmHg

**METHODS (BRIEF DESCRIPTION):**

- Patients were from primary healthcare centers (PHCCs) in four healthcare regions in southern Sweden.
- Swedish patients with hypertension and taking at least one antihypertensive medication were included in the study.
- Exclusion criteria included secondary hypertension, mental impairment or disorders, any terminal illness, or hypertension developed in pregnancy, and impaired vision (not able to read messages on the phone).
- After inclusion, the participants had baseline measurements of vital signs including BP and blood tests including cholesterol, creatinine, HbA1c, and cystatin C. Participants also had to answer questionnaires.
- Patients were randomized 1:1 to either:
  - Interactive web-based self-management system using cell phones
  - Usual care with no home BP monitoring
- Nurses and physicians were given information and instructions on how to use the E-health interactive system.
- All participants were scheduled for follow-up visits at 8 weeks and 12 months.
  - BP and pulse were measured, blood samples were taken, and they answered questionnaires.

**INTERVENTION (# IN THE GROUP):** 482

**COMPARISON (# IN THE GROUP):** 467

**FOLLOW-UP PERIOD:** Eight weeks and 12 months

**RESULTS:**

Primary Outcome –

- At eight weeks:
  - An interactive BP self-management system resulted in more patients with a BP less than 140/90 mmHg compared to control (49% vs 40%, respectively; *P*=.006).
  - An interactive BP self-management system resulted in more patients with a BP less than 130/80 mmHg compared to control (17% vs 13%, respectively; *P*=.034).
- At 12 months:
  - An interactive BP self-management system did not result in more patients with a BP less than 140/80 mmHg compared to control (47% vs 41%, respectively; *P*=.071).
  - An interactive BP self-management system did not result in more patients with a BP less than 130/80 mmHg compared to control (15% vs 14%, respectively; *P*=.856).

**LIMITATIONS:**

- 95% of the participants originated from Sweden, so it was not a heterogenic population therefore outcomes may not apply to all populations.
- The study was not blinded.
- Risk of recruitment bias with individuals already motivated for improvement of their health and may be more technologically adept, compared to someone who may not be technologically adept or motivated for improved self-care.

***Sonia Richards, MD, MPH***
*Northeast Georgia Health System*
*Gainesville, GA*

# No Coughin' with Nalbuphine in Idiopathic Pulmonary Fibrosis

**Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis**

Maher TM, Avram C, Bortey E, et al. Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis. *NEJM Evid.* 2023;2(8):EVIDoa2300083. doi:10.1056/EVIDoa2300083



**KEY TAKEAWAY:** Nalbuphine extended-release (NAL-ER) tablets significantly reduced daytime cough frequency compared to placebo in patients with idiopathic pulmonary fibrosis.

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

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to small sample size, short treatment period, and dropout rate)

**BRIEF BACKGROUND INFORMATION:** There are only two approved medications, both anti-fibrotic, for patients with idiopathic pulmonary fibrosis (IPF), neither of which has shown any effect on cough, a prevalent symptom of the disease. Opioid drugs are commonly used to treat cough symptoms for IPF patients at the end stage of their disease. However, there are no studies that have investigated the therapeutic benefit, particularly on cough, of opioid receptor agonists in these patients during the early stages of IPF due to concern for adverse effects with long-term use.

**PATIENTS:** Adults with idiopathic pulmonary fibrosis and chronic cough

**INTERVENTION:** NAL-ER tablets

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Daytime cough frequency
Secondary Outcome: 24-hour cough frequency, patient-perceived cough severity, patient-perceived daytime cough frequency, patient-perceived breathlessness, physician-perceived change in patient cough

**METHODS (BRIEF DESCRIPTION):**

- Patients were ≥18 years old with definite or probable IPF with no other contributing cause, had at least eight weeks of chronic cough, and whose disease severity was limited to >40% forced vital capacity (FVC) and >25% diffusing capacity of the lung for carbon monoxide (DLCO) in the past six months.
- The participant population was UK-based, majority White, 47% were on antifibrotic therapy, with a mean age of 74 years old and 84% were male.
- Patients were blinded and randomized to one of the following treatments:
  - 22 days of NAL-ER: 27 mg daily, increased to 54 mg twice daily on day five, 108 mg twice daily on day nine, and 162mg/day on day 16 followed by a two-week washout period and then 22 days of placebo.
  - 22 days of placebo followed by a two-week washout period, and then 22 days of NAL-ER treatment (started at 27 mg and up titrated to 162 mg/day by day 16 as above).
- Treatments were administered by blinded physicians.
- The primary outcome was an average change in digital recorder-measured cough frequency (coughs/hr) between waking hours and going to bed (daytime cough frequency).
- Secondary outcomes (measured after day 21 of treatment):
  - Average change in 24-hour cough frequency as measured by digital cough recorder.
  - Patient-perceived cough severity based on the Cough Severity Numerical Rating Scale (CS-NRS) (0 indicated no cough and 10 indicated worst possible cough).
  - Patient-perceived change in daytime cough frequency and breathlessness from baseline by Evaluating Respiratory Symptoms diary (E-RS™:IPF). Scores range from 0–4, with higher scores indicating higher cough frequency.
  - The scale also measures daytime breathlessness. Scores range from 0–23, with higher scores indicating more severe breathlessness.
- Physicians reported their perceived impression of change in patients' cough from baseline using the Clinical Global Impression of Change-Cough scale. Scores range from 1–7. Scores of 1–3 indicate very much improved to minimally improved, a score of four indicates no change, and scores of 5–7 indicate minimal worsening to very much worsened.

**INTERVENTION (# IN THE GROUP):** 21

**COMPARISON (# IN THE GROUP):** 21

**FOLLOW-UP PERIOD:** 44 days

**RESULTS:**

Primary Outcome –

- NAL-ER treatment improved cough frequency reduction compared to placebo (75% vs 23%, respectively; *P*<.001).

Secondary Outcome –

- NAL-ER treatment improved 24-hr cough frequency reduction compared to placebo (51% change, no statistical analysis performed).
- NAL-ER treatment improved mean patient-perceived cough severity (results presented via figure).
- NAL-ER treatment improved mean patient-perceived daytime cough frequency compared to placebo (results presented via figure).
- NAL-ER treatment improved patient-perceived mean daytime breathlessness compared to placebo (results presented via figure).
- NAL-ER treatment improved physician perception of cough in more patients compared to placebo (geometric mean ratio 0.33; 95% CI, 0.18–0.62).

**LIMITATIONS:**

- The patient population was homogenous based outside of the United States with an underrepresentation of females, patients of color, and non-geriatric adults.
- 31% of participants enrolled discontinued treatment due to COVID-19 infection or adverse effects of NAL-ER.
- The sample size was small with only 38 patients.
- Four of the original 42 randomized patients were unaccounted for in the final counts of the patients enrolled.
- The treatment time of the trial was very short, only 22 days, which may limit the true value of adverse effects, opioid dependence, and subsequent withdrawal that long-term opioid therapy for chronic cough might impose.
- There is a general lack of objective pulmonary function data of the test drug on the patient population; we have patient-reported frequency of cough and other patient and provider-reported outcomes but no information on FVC, DLCO, or other objective data to account for NAL-ER's improving cough frequency, which may expose the findings to patient and principal investigator bias.

***Elizabeth Trushaw, MD***
*Cahaba Medical Care FMRP*
*Birmingham, AL*