GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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

**Week of February 21 - 25, 2022**

**SPOTLIGHT: 12 Weeks of Varenicline Monotherapy is Sufficient**

- Does Intermittent Fasting Work for Weight Loss?
- Small Steps, Big Changes
- Effect of Various Exercise Regimens on Peak VO2 Consumption in Patients with HFpEF

# 12 Weeks of Varenicline Monotherapy is Sufficient

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

**Effects of Combined Varenicline with Nicotine Patch and of Extended Treatment Duration on Smoking Cessation: A Randomized Clinical Trial**

Baker TB, Piper ME, Smith SS, et al. Effects of Combined Varenicline with Nicotine Patch and of Extended Treatment Duration on Smoking Cessation: A Randomized Clinical Trial. *JAMA*. 2021; 326(15):1485–1493.



KEY TAKEAWAY: Compared to 12 weeks of varenicline monotherapy, neither the addition of nicotine patches nor extending the duration of treatment improved smoking cessation rates.

STUDY DESIGN: Double-blind, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Tobacco abuse remains a significant public health problem and is the leading cause of preventable death in the United States. Varenicline is considered the most effective treatment available for smoking cessation. However, its effectiveness for sustained smoking cessation at one year is only 20–25%. Trials investigating the effect of extending the duration of treatment or adding nicotine replacement therapy to improve smoking cessation rates have shown mixed results. This study seeks to determine if extending the duration of varenicline therapy or if the addition of nicotine patches improves smoking cessation.

PATIENTS: Adult smokers

INTERVENTION: Extended varenicline treatment, varenicline + nicotine patches, extended varenicline treatment + patches

CONTROL: Varenicline alone

OUTCOME: Smoking abstinence at 52 weeks

Secondary Outcomes: Smoking abstinence at 23 weeks, prolonged abstinence (no smoking at all) from day 7–160, and prolonged abstinence from day 7–352

METHODS (BRIEF DESCRIPTION):

- Study participants were randomized into four groups:
  - Varenicline 1 mg twice a day + placebo nicotine patches for 12 weeks followed by placebo pills/patches for 12 weeks
  - Varenicline 1 mg twice a day + placebo nicotine patches for 24 weeks
  - Varenicline 1 mg twice a day + nicotine 14 mg patches for 12 weeks followed by placebo pills/patches for 12 weeks
  - Varenicline 1 mg twice a day + nicotine 14 mg patches for 24 weeks

INTERVENTION (# IN THE GROUP):

- Varenicline monotherapy + placebo patches for 24 weeks: 311
- Varenicline + nicotine patches for 12 weeks: 314
- Varenicline + nicotine patches for 24 weeks: 311

COMPARISON (# IN THE GROUP): 315

FOLLOW UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Neither the addition of nicotine patches nor extending the duration of treatment improved smoking cessation rates compared to 12 weeks of varenicline monotherapy.
  - Varenicline + nicotine patches did not affect abstinence more than varenicline alone (24 vs 25%, respectively; OR 1; 95% CI, 0.9 to 1.1).
  - Extended varenicline treatment did not affect abstinence more than standard varenicline treatment (25 vs 24%, respectively; OR 1; 95% CI, 0.9 to 1.2).

Secondary Outcomes –

- When comparing extended varenicline treatment or varenicline + nicotine patches to varenicline alone there was no difference in 7-day point prevalence abstinence at 23 weeks nor prolonged abstinence at 160 or 352 days.

LIMITATIONS:

- COVID-19 restrictions caused not all participants to have their self-reported abstinence biochemically confirmed (70%).
- Overall medication adherence declined over the course of the study (40-45% patch adherence; 45-55% pill adherence).
- 9% dropout rate
- 23% of study participants were lost to follow-up.

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# Does Intermittent Fasting Work for Weight Loss?

**Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men with Overweight and Obesity: The TREAT Randomized Clinical Trial**

Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men with Overweight and Obesity: The TREAT Randomized Clinical Trial [published correction appears in *JAMA Intern Med.* 2020 Nov 1;180(11):1555] [published correction appears in JAMA Intern Med. 2021 Jun 1;181(6):883]. *JAMA Intern Med*. 2020 ;180(11):1491–1499.



KEY TAKEAWAY: Time-restricted eating did not cause significantly more weight loss than consistent mealtime eating. However, time-restricted eating resulted in significant weight loss (about 1 kg) at 12 weeks compared to baseline, while consistent mealtime eating did not.

STUDY DESIGN: Individual RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity is a growing epidemic and an independent risk factor for many other diseases. Time-restricted eating (TRE; limiting food and beverage consumption to a specific window of time) has become an increasingly popular dieting method to promote weight loss. However, its efficacy has never been studied in larger-sized clinical trials.

PATIENTS: Adults with BMI 27–43

INTERVENTION: Eating between 12 PM and 8 PM only

CONTROL: Three meals a day with snacks

OUTCOME: Weight loss from baseline

Secondary Outcomes: Between group weight loss, fasting glucose, fasting insulin, HbA1c, lipid profile, systolic blood pressure, diastolic blood pressure

METHODS (BRIEF DESCRIPTION):

- 141 participants were randomized into TRE or consistent-meal timing (CMT) groups.
- The TRE group could eat from 12 PM to 8 PM with no consumption permitted aside from non-caloric beverages during the other 16-hour window.
- The CMT group had three structured meals per day.
- All participants were given a Bluetooth Scale to record their weight every morning.

INTERVENTION (# IN THE GROUP): 69

COMPARISON (# IN THE GROUP): 72

FOLLOW UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- The TRE group had significant weight loss compared to baseline (–0.94 kg; 95% CI, –1.7 to –2.0).
- The CMT group had no significant weight loss compared to baseline (–0.68; 95% CI, –1.4 to 0.05).
- The TRE group and CMT group did not significantly differ in weight loss (–0.26 kg; 95% CI, –1.3 to 0.78).

Secondary Outcomes –

- There was no significant change in within-group or between-group fasting glucose, fasting insulin, HbA1c, lipid profile, or systolic or diastolic blood pressure.

LIMITATIONS:

- Although the study showed no statistically significant difference in weight loss between TRE and CMT, the study was not designed for a direct comparison between them nor for the secondary outcomes in the in-person cohort comparisons.
- Participants did not record consumption intake although the authors state that mathematical modeling showed calorie intake between both groups was similar.
- Adherence was self-reported through surveys.
- Study only lasted 12 weeks.

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**Walking for Hypertension**

Lee LL, Mulvaney CA, Wong YKY, Chan ES, Watson MC, Linn HH. Walking for Hypertension. *Cochrane Database of Syst Rev.* 2021; 2(2):CD008823.



KEY TAKEAWAY: In adults with and without hypertension, moderate intensity walking as regular physical activity may lower systolic blood pressure by 4 to 5 mmHg and may also slightly reduce diastolic blood pressure and heart rate.

STUDY DESIGN: Systematic review and meta-analysis of 73 RCTs (N=5,060)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Hypertension is a major risk factor for cardiovascular disease, stroke, and heart failure. Non-pharmacologic approaches with lifestyle modification, including walking for physical activity, may help prevent or treat hypertension.

PATIENTS: Normotensive and hypertensive adults

INTERVENTION: Supervised walking programs in both community and laboratory (treadmill) settings

CONTROL: No intervention; non-exercising controls

OUTCOME: Systolic blood pressure (SBP)

Secondary Outcomes: Diastolic blood pressure (DB) and heart rate (HR)

METHODS (BRIEF DESCRIPTION):

- The meta-analysis included 73 RCTs with subgroup analysis and assessment of the certainty of evidence.
- Participants included hypertensive and normotensive adults 16–84 years old from 22 countries (male to female ratio=1:1.5).
- Walking interventions varied by:
  - Setting: Indoor (treadmill, outdoor, self-paced, or structured)
  - Intensity: Mostly moderate, as measured by HR, VO2 max, Borg Scale of Perceived Exertion, HR reserve, and mixed methods
  - Frequency: Generally 3 to 5 sessions per week for 20 to 40 minutes (average 153 min/week in 22 studies).
- SBP, DBP, and HR were measured with standard manual or electronic devices, including 24-hour ambulatory BP monitoring devices.
- Mean differences (MD) between baseline and post-intervention blood pressure and heart rate were compared for intervention and control groups.
- Studies with mixed lifestyle interventions (jogging, dietary sodium restriction, etc.) were excluded.

INTERVENTION (# IN THE GROUP): 2,881

COMPARISON (# IN THE GROUP): 2,179

FOLLOW UP PERIOD: Mean 15 weeks (range 4–64)

RESULTS:

Primary Outcome –

- Walking reduced SBP (73 trials, N=5,060; MD –4.1 mmHg; 95% CI, –5.2 to –3.0; moderate-certainty evidence).
- Walking reduced SBP regardless of age.
  - <40 years old: 14 trials, N=491; MD –4.4 mmHg; 95% CI, –6.2 to –2.7; moderate-certainty evidence
  - 41 to 60 years old: 35 trials, N=1,959; MD –3.8 mmHg; 95% CI, –5.6 to –1.9; low-certainty evidence
  - >60 years old: 24 trials, N=2,610; MD -4.3 mmHg; 95% CI –6.2 to –2.4; low-certainty evidence
- Walking reduced SBP regardless of gender.
  - Female: 22 trials, N=1,149; MD –5.7 mmHg; 95% CI –7.9 to –3.4; low-certainty evidence
  - Male: 6 trials, N=203; MD –4.6 mmHg; 95% CI, –8.7 to –0.59; low-certainty evidence

Secondary Outcomes –

- Walking reduced DBP (69 trials, N=4,711; MD –1.8 mmHg; 95% CI, –2.5 to –1.1; low-certainty evidence).
- Walking reduced HR (26 trials; N=1,747; MD –2.8 mmHg; 95% CI, –4.8 to –0.95; low-certainty evidence).

LIMITATIONS:

- Some studies failed to report details of allocation concealment and randomization procedures.
- Inconsistencies in study population and walking interventions.
- Drop-out rates varied, which limited extended data collection.

- Lack of data on long-term effect of walking on blood pressure (only 3 studies measured outcomes months after intervention stopped).

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*The views expressed are those of the authors and do not reflect the official policies or positions of the United States Air Force, the Department of Defense, or the U.S. Government.*

# Effect of Various Exercise Regimens on Peak VO2 Consumption in Patients with HFpEF

**Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients with Heart Failure with Preserved Ejection Fraction**

Mueller S, Winzer EB, Duvinage A, et al. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients with Heart Failure with Preserved Ejection Fraction. *JAMA*. 2021; 325(6):542–551.



KEY TAKEAWAY: High-intensity interval training, moderate continuous training, or guideline-based advice on physical activity does not affect peak VO2 consumption in patients with HFpEF.

STUDY DESIGN: Multisite, non-blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Heart Failure (HF) accounted for 809,000 hospitalizations in the US in 2016. Nearly 50% of those being from HF with preserved ejection fraction (EF). A hallmark of HFpEF is reduced exercise tolerance with a concurrent reduction in quality of life, yet endurance exercise is helpful in improving max exercise capacity as demonstrated by peak oxygen consumption. Different forms of exercise can improve peak oxygen consumption in the general population, but no studies have been performed comparing the benefit of these different forms of exercise in patients with HFpEF.

PATIENTS: Sedentary patients with signs and symptoms of HFpEF

INTERVENTION: High-intensity interval training or moderate continuous training

CONTROL: Guideline control (1-time advice on physical activity according to guidelines)

OUTCOME: Change in peak VO2

Secondary Outcomes: Changes in cardiorespiratory fitness, diastolic function, and BNP

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Sedentary patients with signs/symptoms of HFpEF (exertional dyspnea, LVEF >50%, elevated LV filling pressure associated with BNP >220).
- Patients were randomly assigned 1:1:1 to:
  - High intensity interval training: Three sessions for 38 minutes each, with 10-minute warm-up, 4x4-minute interval training, and three minutes of active recovery
  - Moderate continuous training: Five sessions of 40-minute duration
  - Guideline control: One-time advice on physical activity
- Patients were assessed at baseline, 3 months, 6 months, and 12 months.
  - Assessment included medical history, physical examination, anthropometry, electrocardiogram, blood analysis, cardiopulmonary exercise testing, ECHO and cardiomyopathy questionnaire.
  - The minimal clinical importance for the change in peak VO2 was 2.5 mL/kg/min.
- Individual exercise intensity was determined by repeat cardiopulmonary exercise testing.
- Supervised training was offered three times per week for the first 3 months of the study.
  - For the remaining nine months, training sessions continued at home and were overseen tele-medically.

INTERVENTION (# IN THE GROUP):

- HIIT: 60
- Moderate Exercise: 60

COMPARISON (# IN THE GROUP): 60

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- The change in peak VO2 differed between the groups at three months, but was not clinically significant.
  - High intensity interval training vs guideline control (mean difference 1.5 mL/kg/min; 95% CI, 0.4–2.7)
  - Moderate continuous training vs guideline control (mean difference 2.0 mL/kg/min; 95% CI, 0.9–3.1)
  - High intensity interval training vs moderate continuous training (mean difference –0.4 mL/kg/min; 95% CI, –1.4 to 0.6)

Secondary Outcomes –

- There were no significant differences for changes in any ECHO parameters of diastolic function, BNP levels, or quality of life between groups.

LIMITATIONS:

- Adherence to exercise protocols was fairly limited in this study. Only half of the participants were able to perform at least 70% of the prescribed training sessions during the home-based exercise training months.
- Staff conducting the evaluations were not blinded.
- Lack of exercise ECHO limits the assessment of changes in diastolic function during exercise.
- Multiplicity of analyses limits interpretability of secondary outcomes.

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