GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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

**Week of April 3 - 7, 2023**

**SPOTLIGHT: Role of a Multimodal Opioid-Sparing Protocol to Reduce Opioid Use Post-Operatively**

# Role of a Multimodal Opioid-Sparing Protocol to Reduce Opioid Use Post-Operatively

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

**Effect of a Postoperative Multimodal Opioid-Sparing Protocol vs Standard Opioid Prescribing on Postoperative Opioid Consumption After Knee or Shoulder Arthroscopy: A Randomized Clinical Trial**

NO PAin Investigators. Effect of a postoperative multimodal opioid-sparing protocol vs standard opioid prescribing on postoperative opioid consumption after knee or shoulder arthroscopy: A randomized clinical trial. *JAMA*. 2022;328(13):1326-1335. doi:10.1001/jama.2022.16844



**KEY TAKEAWAY:** A multimodal opioid-sparing pain protocol, consisting of over-the-counter medications and patient education, significantly reduces opioid consumption over six weeks post-operative knee or shoulder arthroscopy.

**STUDY DESIGN:** Multicenter superiority randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Due to the opioid epidemic, there has been increasing interest in opioid-sparing options for pain management. Orthopedic surgeons have been shown to be some of the highest opioid prescribers with significant variability in prescribing practices and excessive prescriptions. There is evidence that non-opioid medications can reduce overall opioid consumption after arthroscopy, but current studies are difficult to apply due to a narrow population, small sample size, or complex postop protocols. Since knee and shoulder arthroscopies are common procedures, it could be beneficial to test a simple opioid-sparing protocol.

**PATIENTS:** Adults post-op from knee or shoulder arthroscopy

**INTERVENTION:** Opioid-sparing protocol

**CONTROL:** Standard protocol

**PRIMARY OUTCOME:** Post-op oral morphine equivalent (OME) consumption

Secondary Outcome: Pain, patient satisfaction, opioid refills, quantity of OMEs present at discharge, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Patients were 64% male with a mean age of 42.7 years old.
- Patients who were scheduled for elective arthroscopic knee or shoulder surgery were recruited from three academic clinical sites in Hamilton, Canada.
- They were randomized immediately prior to surgery to either the opioid-sparing protocol or standard protocol to be initiated at discharge.
- The opioid-sparing protocol consisted of naproxen 500 mg BID PRN, pantoprazole 40 mg, acetaminophen 1,000 mg q6hr PRN, hydromorphone 1 mg rescue prescription q4hr PRN (10 tablets), and patient educational infographic with pain management strategies and risk of opioid misuse.
- Standard care varied by surgeon (20 to 80 tablets of oxycodone, codeine, or hydromorphone as needed).
- Post-op OME consumption was collected by patient-reported medication diary at six weeks.
- Secondary outcomes:
  - Pain was reported using a 100-point visual analog scale with a minimally clinically important difference of 10 and higher scores indicating more pain.
  - Patient satisfaction was reported using modified four-point questions (always, usually, sometimes, never).

**INTERVENTION (# IN THE GROUP):** 95

**COMPARISON (# IN THE GROUP):** 98

**FOLLOW-UP PERIOD:** Six weeks post-operatively

**RESULTS:**

Primary Outcome –

- Opioid-sparing resulted in less OME consumption compared to standard care (8.4 vs 73 mg, respectively; mean difference [MD] 64 mg; 95% CI, 44–84).

Secondary Outcome –

- Opioid-sparing reduced the number of OMEs prescribed at discharge compared to standard care (40 mg vs 341 mg, respectively; MD 301 mg; 95% CI, 269–332).
- There were no differences in pain, patient satisfaction, opioid refills, and adverse events at six weeks.

**LIMITATIONS:**

- There was a risk of bias since neither the patients nor surgeons were blinded to the intervention.
- There was a risk of reporting bias because the measurement of the primary outcome was based on patient-reported opioid consumption.
- Since the specific procedures studied were arthroscopic, the results might not be applicable to more invasive procedures such as joint replacement.
- The participants of the study excluded chronic opioid users, so these results might not be applicable to this patient population.

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*The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, and the Department of Defense.*

# Pharmacologic Interventions for Peripheral Neuropathies

**Pharmacological Management of Painful Peripheral Neuropathies: A Systemic Review**

Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G, Zis P. Pharmacological management of painful peripheral neuropathies: A systemic review. *Pain Ther*. 2021;10(1):55-68. Doi: 10.1007/s40122-020-00210-3.



**KEY TAKEAWAY:** Amitriptyline, duloxetine, gabapentin, pregabalin and venlafaxine are among the first line therapies for peripheral neuropathic pain secondary to diabetes mellitus (DM).

**STUDY DESIGN:** Systematic review of 83 RCTs (N = not available)

**LEVEL OF EVIDENCE:** STEP 2 (downgraded due to no data included in review)

**BRIEF BACKGROUND INFORMATION:** Peripheral neuropathy presents a wide range of symptoms from numbness/tingling to dysesthesias. One of the most common causes of peripheral neuropathy includes DM which affects up to 14% of the adult population in the United States. This sequela of DM may take many visits and adjustments of medications to properly manage.

**PATIENTS:** Patients with diabetic peripheral neuropathy

**INTERVENTION:** Neuropathic pain medications

**CONTROL:** Other pharmacologic management of placebo

**PRIMARY OUTCOME:** Peripheral neuropathic pain symptoms

Secondary Outcome: Peripheral neuropathic pain symptoms due to other disease processes such as HIV and chemotherapy

**METHODS (BRIEF DESCRIPTION):**

- Demographic information was cross-referenced to ensure similar groups of patients; however, the demographics were not explicitly stated.
- Inclusion criteria: Human subjects, full text in English, pharmacological RACTs, adequate methodological quality
- Exclusion criteria: No references to peripheral neuropathy, not an original study, pain relief not primary aim, less than 10 patients per treatment arm, withdrawal study, non-pharmacological trial
- Quality of studies were screened using the Jadad scoring system (trials with scores <4 were excluded). Those included were then assessed with the Cochrane Collaboration risk of bias assessment tool.
- The compiled studies looked at different medical interventions in the alleviation of peripheral neuropathy of different etiologies.
    - Medications that were investigated: SNRIs, SSRIs, TCAs, opioids, topicals, anti-convulsants
- Studies varied in determining and measuring primary and secondary outcomes. No specification was explicitly stated.

**INTERVENTION (# IN THE GROUP):** Not available

**COMPARISON (# IN THE GROUP):** Not available

**FOLLOW-UP PERIOD:** Not available

**RESULTS:**

Primary Outcome –

- The following medications reduced peripheral neuropathy due to diabetes (DPN):
    - Best evidence as monotherapy: Amitriptyline, Duloxetine, Gabapentin, Pregabalin, Venlafaxine
    - Other options as monotherapy: Dextromethorphan/quinidine, Isosorbide dinitrate spray, Maprotiline, Lacosamide, Tanexumab
    - Effective as add-ons for DPN: Botulinum Toxin type A, Capsaicin 8% patch, Cebranopadol, Citrullus colocynthis, Oxycodone

Secondary Outcome –

- The following medications reduced peripheral neuropathy due to HIV (HIVPN) and chemotherapy (CIPN):
    - HIVPN monotherapy: Gabapentin
    - Effective add-ons for HIVPN: Capsaicin 8% patch, delta-9-tetrahydrocannabinol, Lamotrigine
    - Effective add-ons for CIPN: Duloxetine

**LIMITATIONS:**

- The study only included publications in PubMed and clinicaltrials.gov.
- There was not one set of diagnostic criteria that was used in all studies.
- No meta-analysis was completed.
- No specific information, such as sample size, data, and statistical significance, was available in the systematic review.

- Lack of clarification for different types of diabetes.

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# Guanfacine Extended-Release for Adult Attention-Deficit/Hyperactivity Disorder

**Efficacy and Safety of Guanfacine Extended-Release in the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: Results of a Randomized, Double-Blind, Placebo-Controlled Study**

Iwanami A, Saito K, Fujiwara M, Okutsu D, Ichikawa H. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults: Results of a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2020 Apr 14;81(3):19m12979. doi: 10.4088/JCP.19m12979.



**KEY TAKEAWAY:** Guanfacine extended-release significantly decreases attention-deficit/hyperactivity disorder (ADHD) symptoms in adults.

**STUDY DESIGN:** Double-blind randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** ADHD in adults has fewer approved treatment options than in children. Guanfacine is an approved antihypertensive medication that has approval for the treatment of ADHD in children. Few studies have been performed to test the efficacy of guanfacine in adults. Yet, is it not an FDA-approved treatment for ADHD in adulthood.

**PATIENTS:** Adults with ADHD

**INTERVENTION:** Guanfacine extended-release

**CONTROL:** Placebo

**PRIMARY OUTCOME:** ADHD symptoms

Secondary Outcome: Quality of life, executive function, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Demographic characteristics: Japanese adults, average age 32 years old, 64.5% male, no comorbid severe mental health disorders or cardiovascular disease
- Patients were blinded and randomized into:
  - Intervention: Guanfacine extended-release titrated for five weeks, maintained for five weeks, then tapered for two weeks
  - Control: Placebo pill titrated in the same manner
- The primary outcome was measured via the ADHD-Rating Scale IV with adult prompts (ADHD-RS-IV). The scale ranged from 0 to 54 with higher scores reflecting a greater severity of symptoms. ADHD-RS-IV was administered every week including during screening.
- Quality of life was measured with the Adult ADHD Quality of Life Questionnaire (AAQoL) with a scale from 0 to 100 and higher scores indicating greater quality of life.
- Executive function was measured using the Behavior Rating Inventory of Executive Function-Adult Version (BREIF-A) with a scale from 0 to 100 with higher scores indicating greater dysfunction.
- AAQoL and BRIEF-A were administered at screening, midway (week 6), and discontinuation (week 12).
- Treatment-emergent adverse events (TEAE) and serious adverse events were monitored throughout the study.

**INTERVENTION (# IN THE GROUP):** 101

**COMPARISON (# IN THE GROUP):** 100

**FOLLOW-UP PERIOD:** 13 weeks or the week after discontinuation

**RESULTS:**

Primary Outcome –

- Guanfacine extended-release significantly reduced ADHD symptoms compared to placebo (–12 vs –7.3, respectively; mean difference [MD] –4.3; 95% CI, –6.7 to –1.9).

Secondary Outcome –

- There were no clinically significant differences in quality of life and executive function between the Guanfacine extended-release and placebo.
- Overall instances of TEAEs, including those leading to discontinuation, were higher for guanfacine than placebo (82 vs 62 events, respectively; no P-value reported).
  - Most common TEAEs were somnolence, thirst, and blood pressure decrease.
  - TEAEs leading to withdrawal from the study were more common with guanfacine than placebo (20% vs 3.0%, respectively; no P-value reported).

**LIMITATIONS:**

- The patient population was homogenous as they were all Japanese. Thus, the findings may not be generalized to other populations.

- The age distribution was imbalanced, with the majority <30 years old in the guanfacine group and the majority ≥40 years old in the placebo group.

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# Is Mindfulness-Based Stress Reduction as Effective as Escitalopram for the Treatment of Anxiety Disorders?

**Mindfulness-Based Stress Reduction vs Escitalopram for the Treatment of Adults with Anxiety Disorders: A Randomized Clinical Trial**

Hoge EA, Bui E, Mete M, Dutton MA, Baker AW, Simon NM. Mindfulness-Based Stress Reduction vs Escitalopram for the Treatment of Adults with Anxiety Disorders: A Randomized Clinical Trial. *JAMA Psychiatry*. 2023; 80(1):13-21. doi:10.1001/jamapsychiatry.2022.3679



**KEY TAKEAWAY:** Mindfulness-Based Stress Reduction (MBSR) is non-inferior to Escitalopram for anxiety disorder treatment.

**STUDY DESIGN:** Randomized, single-blinded, controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Anxiety disorders are the most common mental disorders and are associated with significant distress, daily functioning impairment, and suicide risks. The current standard of treatment includes a pharmacological approach and CBT. Each has disadvantages such as the side effect profiles and the need to take medicine daily (pharmacological) or lack of access to trained providers (CBT). Mindfulness-Based Stress Reduction (MBSR) is much more accessible, but until now there have been no trials comparing MBSR to Escitalopram for the reduction of anxiety.

**PATIENTS:** Adults with a primary diagnosis of anxiety disorder

**INTERVENTION:** MBSR

**CONTROL:** Escitalopram

**PRIMARY OUTCOME:** Anxiety levels

**METHODS (BRIEF DESCRIPTION):**

- Participants 18 to 75 years old, were recruited from three urban academic medical centers in the US, with a primary diagnosis of generalized anxiety disorder, social anxiety disorder, panic disorder, or agoraphobia with clinically significant severity of the disorders.
- Patients were equally randomized to one of the following treatments:
  - MBSR (breath awareness, body scan, mindful movement) for eight weeks including:
    - 45-minute daily home practice exercises
    - A day-long retreat during the fifth or sixth week
    - 2.5 hour-long weekly classes
  - Escitalopram for eight weeks with medication management visits at weeks one, two, four, six, and eight.
    - The initial dose was 10 mg/day. At week two the dose was increased to 20 mg/day if tolerated.
- MBSR was taught by qualified instructors. Audio recordings from sessions were reviewed by a qualified MBSR instructor.
- Attendance was self-reported to the study clinician or recorded by the MBSR teacher.
- Adherence with Escitalopram was measured by self-report and pill count.
- Clinical Global Impression of Severity scale (CGI-S) for anxiety was used to measure primary outcome.
  - The scale ranged from 1 (normal) to 7 (among the most severely ill).
  - A predefined noninferiority margin of -0.495 was used to compare the effectiveness of MBSR with Escitalopram.

**INTERVENTION (# IN THE GROUP):** 102

**COMPARISON (# IN THE GROUP):** 106

**FOLLOW-UP PERIOD:** Eight weeks

**RESULTS:**

Primary Outcome –

- MBSR is non-inferior to Escitalopram for anxiety treatment (mean difference 0.08; 95% CI, –0.038 to 0.23).

**LIMITATIONS:**

- Limited generalizability due to the predominantly female population (75%), a lack of data on anxiety disorder chronicity in patients, and recruitment at only three urban academic centers.
- The MBSR group was engaged in treatment-related activities more often than the Escitalopram group.

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## *Helicobacter pylori* Eradication for Primary Prevention of Peptic Ulcer Bleeding in Older Patients Prescribed Aspirin in Primary Care (HEAT): A Randomised, Double-Blind, Placebo-Controlled Trial

Hawkey C, Avery A, Coupland CA, et al. *Helicobacter pylori* eradication for primary prevention of peptic ulcer bleeding in older patients prescribed aspirin in primary care (heat): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2022;400(10363):1597-1606. doi:10.1016/s0140-6736(22)01843



**KEY TAKEAWAY:** Primary *Helicobacter pylori* (*H. pylori*) eradication protects against aspirin-associated peptic ulcer bleeding in adults 60 years and older.

**STUDY DESIGN:** Multi-site, randomized, double-blinded, placebo-controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Aspirin is commonly prescribed for primary and secondary prevention of cardiovascular disease. It also increases the risk of peptic ulcer bleeding. Previous studies have investigated *H. pylori* eradication for the secondary prevention of recurrent ulcer bleeding prevention with mixed results.

**PATIENTS:** Older adults on daily aspirin

**INTERVENTION:** Primary eradication of *H. pylori* through Lansoprazole, Clarithromycin, and Metronidazole

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Time to hospitalization or death due to peptic ulcer bleeding

Secondary Outcome: Other GI bleeding, thrombotic cardiovascular events, non-bleeding ulcers, consultations for dyspepsia, time to first prescription for PPI/anti-ulcer/dyspepsia medication

**METHODS (BRIEF DESCRIPTION):**

- Adults at least 60 years old receiving aspirin ≤325 mg/day with positive *H. pylori* C13 urea breath test were randomly assigned in a 1:1 ratio into treatment and control groups.
- Treatment included Lansoprazole 30 mg, Clarithromycin 500 mg, and Metronidazole 400 mg twice a day for one week.
- The control group received placebo corresponding to the three active medications.
- The outcomes were identified with searches utilizing multiple databases: hospital episode statistics, Office for National Statistics mortality data, general practice databases using MIQUEST software, patient and general practice spontaneous reports
- Episodes that mentioned GT bleeding or peptic ulcer were evaluated by a masked adjudication committee consisting of three specialist clinicians.

**INTERVENTION (# IN THE GROUP):** 2,677

**COMPARISON (# IN THE GROUP):** 2,675

**FOLLOW-UP PERIOD:** Seven years and 9.5 months

**RESULTS:**

Primary Outcome –

- Primary eradication of *H. pylori* prevented peptic ulcer bleeding within 2.5 years compared to placebo HR 0.35 (95% CI, 0.14–0.89; NNT=238).
  - 6 vs 17 episodes, respectively (rate 0.92; 95% CI, 0.41–2.0)
  - Event rates 0.92% vs 2.6%, respectively
- Beyond 2.5 years, there were no significant differences between the groups (HR 1.3; 95% CI, 0.55–3.1).

Secondary Outcome –

- Primary eradication of *H. pylori* prevented gastric and duodenal ulcer bleeding compared to placebo within 2.5 years (HR 0.31; 95% CI, 0.11–0.85).
  - Beyond 2.5 years, there were no significant differences (HR 1.1; 95% CI, 0.43–2.9).
  - Cox proportional hazards assumption was not met (Schoenfeld test *P*=.012).
- There were no significant differences between the two groups and Cox proportional hazards assumptions were not met for all other secondary outcomes.

**LIMITATIONS:**

- The study did not assess other over-the-counter or prescription drugs patients were taking.
- The low rate of outcome events led to the early termination of the study.
- No confirmatory testing was completed for *H. pylori* eradication.

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*The views expressed in this GEM are those of the author and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.*

# The Effect of Lifestyle Modifications in Improving Uncontrolled Hypertension Among Black Adults

**Effect of Lifestyle Coaching or Enhanced Pharmacotherapy on Blood Pressure Control Among Black Adults with Persistent Uncontrolled Hypertension: A Cluster Randomized Clinical Trial**

Nguyen-Huynh MN, Young JD, Ovbiagele B, et al. Effect of Lifestyle Coaching or Enhanced Pharmacotherapy on Blood Pressure Control Among Black Adults with Persistent Uncontrolled Hypertension: A Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(5):e2212397. Published 2022 May 2. doi:10.1001/jamanetworkopen.2022.12397



**KEY TAKEAWAY:** Lifestyle coaching interventions are not more effective in controlling blood pressure than usual care at 12 months but may be more effective at 24 and 48 months. Enhanced pharmacotherapy was no different than lifestyle coaching interventions or usual care.

**STUDY DESIGN:** Cluster randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** The incidence of cardiovascular disease among Black patients is higher compared to White Americans. Hypertension is a major modifiable risk factor for cardiovascular disease, and hypertension rates are higher among the Black population. There is a disparity in blood pressure control among these populations, and lifestyle intervention is a fundamental part of hypertension treatment in both populations.

**PATIENTS:** Adult Black Americans with hypertension

**INTERVENTION:** Lifestyle coaching intervention or enhanced pharmacotherapy monitoring protocol

**CONTROL:** Usual care

**PRIMARY OUTCOME:** BP control at 12 months

Secondary Outcome: BP control at 24 and 48 months

**METHODS (BRIEF DESCRIPTION):**

- Disparities exist between Black and White patients in the Kaiser panel.
  - Black adults experience a higher burden of cardiovascular disease, stroke, and hypertension.
  - Prior studies have indicated Black patients experience worst blood pressure control compared with patients of other races and ethnicities, even when healthcare resources provided are equal.
- The patient population included adult Black Americans at Kaiser Permanente Oakland Medical Center who were listed in the hypertension registry with sufficient understanding of English.
- Participants were randomized into one of three groups:
  - Usual care (UC): Usual blood pressure (BP) measurement and medication adjustment (free BP checks reviewed by primary care providers to adjust medications)
  - Enhanced pharmacotherapy (EP): Usual care + BP checks with optimization of thiazide diuretics and spironolactone for hypertension and patient education
  - Lifestyle coaching (LC): 16 telephone coaching sessions with dietician using motivational interviewing to achieve DASH diet and education
- The groups were similar with respect to age, BMI, smoking status, median household income, and comorbidities.
- Controlled BP was defined as <140/90 mmHg.
- BP measurements closest to 12 months after enrollment were used.

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

- Lifestyle coaching interventions: 286
- Enhanced pharmacotherapy: 346

**COMPARISON (# IN THE GROUP):** 1,129

**FOLLOW-UP PERIOD:** 48 months

**RESULTS:**

Primary Outcome –

- BP control was not significantly different between any group at 12 months.
  - EP vs UC (223 vs 698 patients, respectively; *P*=.44)
  - EP vs LC (223 vs 194 patients, respectively; *P*=.36)
  - LC vs UC (194 vs 698, respectively; *P*=.07)

Secondary Outcome –

- LC improved BP control more than UC alone at 24 months (72% vs 61% , respectively; *P*=.001).

    - BP control was not significantly different between EP and UC or EP and LC at 24 months.
- LC improved BP control more than UC at 48 months (209 vs 728 patients, respectively; *P*=.006).
    - BP control was not significantly different between EP and UC or EP and LC at 48 months.

**LIMITATIONS:**

- The generalizability was limited due to all participants being in the Kaiser health system with pharmacy benefits and access to care.
- Dichotomous measurements did not consider all available BP measurements.
- LC group had a lower response rate to instruments rating DASH diet and lifestyle modifications, so the exact influence on BP control is not specific.
- It was not clear if the LC also was receiving usual care so we can't say if LC is more effective than UC or the addition of LC to UC is more effective than UC alone.
- This trial did not account for health care disparities of the included population. Justice requires health disparities to be addressed outside of the medical system, such as in law, politics, government, and society at large. Racism and discrimination should be improved systematically and on an individual basis to improve social determinants of health such as systemic racism, income, education, and location of residence.

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# Does Ivermectin Decrease Length of Time to Recovery in COVID-19 Patients?

**Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients with Mild to Moderate COVID-19: A Randomized Clinical Trial**

Naggie S, Boulware DR, Lindsell CJ, et al. Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19. *JAMA*.2022;328(16):1595. doi:10.1001/jama.2022.18590



**KEY TAKEAWAY:** Ivermectin does not improve time to recovery in outpatients at least 30 years old with mild-to-moderate COVID-19 infection.

**STUDY DESIGN:** Multi-site, double-blind, placebo-controlled, randomized control trial within a platform protocol

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Several medications were postulated to effectively treat COVID-19 early in the pandemic. Ivermectin gained particular attention in popular culture due to an early in-vitro study showing antiviral activity. Very little high-quality evidence has been published to support or refute the use of Ivermectin in the treatment of mild-moderate COVID-19.

**PATIENTS:** Adult outpatients with mild-moderate COVID-19 for ≤7 days

**INTERVENTION:** Ivermectin for three days

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Time to sustained recovery

Secondary Outcome: Hospitalization or death, symptom improvement, mean time spent with illness, emergency or urgent care visit

**METHODS (BRIEF DESCRIPTION):**

- Vaccinated and unvaccinated adults at least 30 years old with at least two symptoms of COVID with mild-moderate symptoms and a positive PCR or antigen test were included.
  - The exclusion criteria included hospitalization, allergy, end-stage renal disease, liver failure, pregnancy, nursing, and concomitant use of contraindicated medications.
  - 47.1% of study group participants were fully vaccinated.
  - 47.6% of control group participants were fully vaccinated.
- Patients were blinded and randomized into one of the investigational drugs in the platform protocol or placebo.
  - This trial only included data for the Ivermectin group.
  - The comparison group included control patients for other protocol drugs so long as they were also eligible for the Ivermectin group.
- Patients were sent 15 7 mg Ivermectin capsules or a matched placebo by mail from a central pharmacy. They were given specific instructions on a weight-based dose to approximate 400 µg/kg daily with a max dose of 35 mg daily.
  - Study day one was defined as the day the mail was received.
- Patients submitted online daily reports up to day 14, then at spaced intervals until day 28 or until they had three consecutive days without symptoms.
- Symptom severity was measured with a COVID-19 Ordinal Outcome Scale via patient daily reporting.

**INTERVENTION (# IN THE GROUP):** 817

**COMPARISON (# IN THE GROUP):** 774

**FOLLOW-UP PERIOD:** 28 days

**RESULTS:**

Primary Outcome –

- There was no between-group difference in the mean time to recovery for Ivermectin vs placebo (12 vs 13 days, respectively; HR 1.1; 95% CrI, 0.96–1.2).

Secondary Outcome –

- There were no significant differences in secondary outcomes between ivermectin vs placebo:
  - Mortality in the Ivermectin and placebo groups were too low to statistically compare (1 and 0, respectively).
  - Hospitalization through day 28 (10 and 9, respectively; HR 1.1; 95% CrI, 0.4–2.6).
  - Hospitalization, ED visit, urgent care visit, or death through day 28 (32 and 28, respectively; HR 1.2; 95% CrI, 0.6–1.8).
  - Difference in Clinical Progression was not statistically significant between Ivermectin and placebo groups at 28 days(OR 1.1; 95% CrI, 0.52–1.9).

- Mean time unwell (10.96 vs 11.45, respectively; HR –0.49; 95% CrI, –0.82 to –0.15).

**LIMITATIONS:**

- Study group participants did not receive their Ivermectin until day six of illness on average.
- A significant portion of the study group (42%) did not receive the full 400 µg/kg daily dose of Ivermectin due to weight >88 kg and a maximum dose of 35 mg daily.
- The sample population was relatively homogenous (81% identified as White).
- The clinical progression of the disease was only reported in aggregate and not separated by treatment.

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