GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

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FPIN
Family Physicians Inquiries Network

Volume 6 Issue 20

More Isn't Always Better: Aspirin Added to Anticoagulation

Aspirin in Patients with Chronic Coronary Syndrome Receiving Oral Anticoagulation

Lemesle G, Didier R, Steg PG, et al. Aspirin in Patients with Chronic Coronary Syndrome Receiving Oral Anticoagulation. *N Engl J Med*. 2025;393(16):1578-1588. doi:10.1056/NEJMoa2507532

KEY TAKEAWAY: In patients with chronic coronary syndrome at high risk for atherothrombotic events who were receiving an oral anticoagulant, the addition of aspirin led to a higher risk of myocardial infarction (MI), cardiovascular death, stroke, systemic embolism, major bleeding or death from any cause compared to placebo.

STUDY DESIGN: Multicenter, double-blind, placebo-controlled randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The addition of aspirin to an anticoagulant in patients with chronic coronary syndrome at high risk for atherothrombotic events is the current mainstay of medical guidelines. This study aimed to further explore the efficacy of this combination therapy on the patient's overall mortality and morbidity.

PATIENTS: Adults with coronary syndrome at high risk of atherothrombotic events

INTERVENTION: Aspirin + oral anticoagulant

CONTROL: Placebo + oral anticoagulant

PRIMARY OUTCOME: Composite of cardiovascular death, MI, stroke, coronary revascularization, systemic embolism, or acute limb ischemia

Secondary Outcome: Efficacy and safety outcomes

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from 51 facilities in France.
- Patients were eligible if they were ≥18 years old, had chronic coronary syndrome, and currently receiving oral anticoagulation therapy.
- Patients were randomly assigned in a 1:1 ratio to receive 100 mg of aspirin daily or placebo, with all patients receiving their current anticoagulation.
- Patient visits were scheduled every six months during follow up.
- The primary outcome was measured using the Cox Frailty Model and hazard ratios comparing the number of atherothrombotic events that occurred in the intervention compared to the control group.
- The secondary outcome was measured using the same methods to compare the difference in all-cause mortality and bleeding risk between the two groups.

INTERVENTION (# IN THE GROUP): 433

COMPARISON (# IN THE GROUP): 439

FOLLOW-UP PERIOD: 2.2 years

RESULTS:

Primary Outcome –

- Adding aspirin to oral anticoagulants increased the risk of composite cardiovascular death, MI, stroke, systemic embolism, coronary revascularization, or acute limb ischemia compared to the addition of placebo (adjusted hazard ratio [aHR] 1.5; 95% CI, 1.1–2.2).

Secondary Outcome –

- Adding aspirin to an oral anticoagulant increased the risk of death from any cause compared to the addition of placebo (aHR 1.7; 95% CI, 1.1–2.6).
- Adding aspirin to an oral anticoagulant increased the risk major bleeding compared to the addition of placebo (aHR 3.4; 95% CI, 1.9–6.0).

LIMITATIONS:

- Early termination of the trial could have limited the investigation into the superiority of dual-pathway therapy for atherothrombotic events.
- All centers were in a single country, thus limiting the generalizability to other health care systems.
- The study was performed during the COVID-19 pandemic, which limited enrollment.
- The sample was predominantly men, limiting the generalizability to women.

Andrew M Peterson, DO
Southern Illinois University (Quincy) Program
Quincy, IL

How Does Osteopathic Manipulation Medicine Affect Mind, Body, and Spirit?

Effects of Manual Osteopathic Interventions on Psychometric and Psychophysiological Indicators of Anxiety, Depression and Stress in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Gordon TC, Hope-Bell J, Draper-Rodi J, MacMillan A, Miller D, Edwards DJ. Effects of Manual Osteopathic Interventions on Psychometric and Psychophysiological Indicators of Anxiety, Depression and Stress in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *BMJ Open*. 2025;15(2):e095933. Published 2025 Feb 7. doi:10.1136/bmjopen-2024-095933

KEY TAKEAWAY: Osteopathic interventions show significant effects on reducing depression, increasing skin conductance, and improving depression in pain populations.

STUDY DESIGN: Systematic review and meta-analysis of 20 randomized controlled trials (RCTs) (N=1,736)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to wide prediction intervals and moderate heterogeneity, indicating uncertainty in true effect sizes)

BRIEF BACKGROUND INFORMATION: Systematic reviews in the past have either shown the positive effects of osteopathic manipulation medicine (OMM) on patients' autonomic nervous system or have shown how OMM can reduce psychological symptoms. However, there has been no meta-analysis of RCTs studying the effects of OMM on psychophysiology and mental health. This study focused on the effectiveness of osteopathic interventions for improving psychophysiological indicators and psychological psychometric outcomes relating to mental health in adult populations.

PATIENTS: Adults >18 years old

INTERVENTION: Osteopathic and related manual interventions

CONTROL: No intervention or placebo (sham interventions)

PRIMARY OUTCOME: Psychophysiological outcomes and mental health outcomes

METHODS (BRIEF DESCRIPTION):

- Studies were searched using the following databases: Pubmed, MEDLINE via Ovid, Scopus, Cochrane and AMED from database inception to September 2024.
- Inclusion criteria:
  - RCTs with >30 participants
  - Healthy individuals without diagnosed medical, psychological, or pain conditions.
  - Individuals without pain, but had formal diagnosis of anxiety, stress, or depression.
  - Individuals with pain with corresponding anxiety, depression, or stress.
- Studies that used osteopathic interventions (hands on treatment such as high velocity, low amplitude [HVLA], myofascial release [MFR], craniosacral, etc.) and compared them to no osteopathic interventions, a placebo, or sham interventions (such as light touch or relaxation techniques) were also included.
- Frequency of treatment and the duration of treatment were not explicitly measured.
- Populations were excluded that could confound outcomes, such as populations with Alzheimer's, dementia, brain injuries, or populations with ongoing cancer treatments or individuals who were pregnant.
- 14 studies focused on psychophysiological outcomes like heart rate variability (HRV) and skin conductance (SC).
  - HRV measured the variation between consecutive heartbeats, the higher the HRV indicating increased parasympathetic activation and relaxation.
  - SC used electrodes to detect sweat gland activity, where the higher the SC indicated an increase in sympathetic nervous system activation, which was associated with autonomic regulation and reduction of the experience of pain.
- Six studies focused on psychometric outcomes like depression, anxiety, stress, and well-being.
  - Depression was assessed using measures such as Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS), with higher scores indicating increased depression.

    - Anxiety was assessed using measures such as Hamilton Anxiety Rating Scale (HARS) and State-Trait Anxiety Inventory (STAI), with higher scores indicating more anxiety.
    - Stress was assessed using measures such as Perceived Stress Scale (PSS), with higher scores indicating more stress.
    - Well-being was assessed using measures such as the General Well-Being Schedule (GWB), with lower scores indicating more distress.
- Five main meta-analysis were conducted and one subgroup analysis for patients with pain and those without pain for the following outcomes:
    - Psychometric self-reported depression scores, with higher scores indicating more depression
    - Psychometric self-reported anxiety scores, with higher scores indicating higher anxiety
    - Psychophysiological HRV as measured by two different techniques root square mean of successive differences of normal heartbeats (RMSSD) and frequency-domain sympathovagal balance of the low-frequency/high-frequency (LF/HF) ratio.
    - Psychophysiological SC
- Risk of bias was methodically assessed by three reviewers (JH-B, AM and DM) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for RCTs; studies without clear randomization were excluded.
- Meta-analysis utilized mean post-intervention scores, standard deviation, and sample sizes to compare standardized mean differences using Hedges' g with 95% CI.
- Overall effect (computed as Hedges' g) was calculated, with a negative Hedges' g for symptoms indicating that the intervention had a greater reduction in symptoms compared to the control.
- I^2 determined statistical heterogeneity: 0–24% indicated low heterogeneity, 25–49% low, 50–74% moderate, and >75% high heterogeneity.

INTERVENTION (# IN THE GROUP):

- Six psychometric studies: 392
- 14 psychophysiological studies: 752

COMPARISON (# IN THE GROUP):

- Six psychometric studies: 186
- 14 psychometric studies: 406

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- OMT lowered depression scores compared to no treatment or placebo (5 studies, n=338; Hedges' g –0.47; 95% CI, –0.86 to –0.09; I^2=58%).
- OMT lowered depression scores for patients experiencing pain (2 studies, n=108; Hedges' g –0.61; 95% CI, –1.1 to –0.17; I^2=55%).
- OMT lowered postintervention depression scores for patients with anxiety (non-pain) (3 studies, n=230; Hedges' g –0.23; 95% CI, –0.91 to 0.46; I^2=56%).
- OMT resulted in lower postintervention anxiety scores (3 studies, n=197; Hedges' g –0.15; 95% CI, –0.51 to 0.20; I^2=0%).

Secondary Outcome –

- OMT increased skin conductance responses (5 studies, n=190; Hedges' g 0.67; 95% CI, 0.0–1.3; I^2=75%).
- OMT resulted in higher postintervention scores for HRV (2 studies, n=188; Hedges' g 0.11; 95% CI, –0.29 to 0.51; I^2=39%).
- OMT showed small to moderate effect on postintervention scores for HRV as measured by LF/HR ratio (4 studies, n=264; Hedges' g –0.36; 95% CI, –0.80 to 0.08; I^2=59%).

LIMITATIONS:

- Moderate heterogeneity along with wide confidence intervals suggest uncertainty in true effect sizes.
- 18 out of 41 studies did not clarify the randomization of procedures, questioning validity of the status of RCTs and exclusion.
- Only English studies were included, introducing language bias.
- Most studies only focused on short-term effects of OMM compared to studying long-term effects.

Gabriella Shirazi, DO
Loyola MacNeal Hospital
Berwyn, IL

Does It Matter? Anterior vs Posterior Approach in Treating Adhesive Capsulitis

Targeting the Sweet Spot: A Systematic Review with Meta-Analysis of Anterior vs Posterior Glenohumeral Joint Injections for Adhesive Capsulitis

Rhim HC, Schon JM, Xu R, et al. Targeting the Sweet Spot: A Systematic Review with Meta-Analysis of Anterior Versus Posterior Glenohumeral Joint Injections for Adhesive Capsulitis. *Clin J Sport Med*. 2025;35(1):1-12. doi:10.1097/JSM.0000000000001228

KEY TAKEAWAY: In patients with adhesive capsulitis, corticosteroid injection reduces pain regardless of approach but an anterior approach may result in improved range of motion.

STUDY DESIGN: Systematic review and meta-analysis of six randomized controlled trials (RCTs) and one prospective cohort study (N=468)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample size, short follow-up, and lack of blinding)

BRIEF BACKGROUND INFORMATION: Adhesive capsulitis is a condition that is commonly seen in the primary care clinic. It results in significant pain and disability, primarily due to decreased range of motion. This study aimed to investigate whether the approach of corticosteroid injection affected pain relief and improvement in range of motion.

PATIENTS: Adults with adhesive capsulitis

INTERVENTION: Corticosteroid injection into the glenohumeral joint via an anterior approach

CONTROL: Corticosteroid injection into the glenohumeral joint via a posterior approach

PRIMARY OUTCOME: Pain and range of motion (ROM) at 12 weeks

Secondary Outcome: Pain at eight weeks, function at 12 weeks, accuracy, adverse events

METHODS (BRIEF DESCRIPTION):

- Articles were searched on MEDLINE, Embase, Web of Science and Cochrane Center Register of Controlled Trials per the PRISMA guidelines.
- Average Demographic: Asian countries, 60% female
- RCTs and prospective comparative studies, and adults with adhesive capsulitis without other causes of shoulder pain were included in the study.
- Studies utilizing both anterior and posterior injections in the same patient or extra-articular injections were excluded from the study.
- Individuals received a single corticosteroid injection (40 mg methylprednisolone or 40 mg triamcinolone) into the glenohumeral joint via an anterior approach under ultrasound guidance or using landmark-based approach.
- Individuals received a single corticosteroid injection (40 mg methyl-prednisolone or 40 mg triamcinolone) into the glenohumeral joint via a posterior approach under ultrasound guidance or using landmark-based approach.
- The primary outcomes measured pain and ROM at 12 weeks.
  - Pain VAS at 12 weeks was measured using standardized mean difference (SMD).
    - Small effect: SMD 0.2
    - Medium effect: SMD 0.5
    - Large effect: SMD 0.8
  - Difference in degrees of ROM was measured using a weighted mean difference (WMD). Higher values indicate a greater improvement in ROM.
- The following were measured as the secondary outcomes:
  - Pain VAS at eight weeks was measured using SMD.
  - Function at 12 weeks was assessed using the following tools:
    - American Shoulder and Elbow Scores (ASES)
    - Constant-Murley shoulder Score (Constant)
    - Shoulder Pain and Disability Index (SPADI)
  - Accuracy was measured by calculating overall pooled estimate.
  - Adverse events were measured by the overall incidence. Major complications were not specifically defined in the study. Minor complications included transient local pain, sweating, and facial flushing.

INTERVENTION (# IN THE GROUP): 241

COMPARISON (# IN THE GROUP): 227

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- There was no statistically significant difference in pain at 12 weeks between an anterior compared to a posterior approach (6 studies, SMD –0.86; 95% CI, –1.8 to 0.04).
- An anterior approach improved external rotation (WMD 8.1; 95% CI, 0.79–15) and abduction (WMD 6.8; 95% CI, 3.1–10).
- There was no significant improvement in forward flexion (WMD 5.9; 95% CI, 20–12) or internal rotation (SMD 20; 95% CI, 20–0.13).

Secondary Outcome –

- There was no significant difference in pain at eight weeks, function at 12 weeks, or accuracy between the approaches.
- There were no major adverse effects reported.

LIMITATIONS:

- The studies only followed the patients for 12 weeks; adhesive capsulitis often affects patients for 6 months to several years.
- The studies were primarily completed in Asian countries which may decrease generalizability to US patient populations.
- Some studies used ultrasound guided injections while some used landmark-based injections.
- The doses and makeup of the injections varied between studies, though all contained a corticosteroid.
- Due to the nature of the interventions, participants were not blinded.

Kaleb Kremsreiter, MD
David Grant Medical Center Travis AFB FMR
Fairfield, CA

The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Air Force, Defense Health Agency, Department of Defense, or the U.S. Government.

Does Use of Muscle-Building Supplements Lead to Anabolic Steroid Use?

Anabolic Steroid Initiation Among Boys and Young Men After Use of Muscle-Building Supplements

Bulens A, Calzo JP, Eik-Nes TT, et al. Anabolic Steroid Initiation Among Boys and Young Men After Use of Muscle-Building Supplements. *JAMA Netw Open*. 2024;7(12):e2450566. Published 2024 Dec 2. doi:10.1001/jamanetworkopen.2024.50566

KEY TAKEAWAY: Patients have a significantly increased likelihood of using anabolic-androgenic steroids within 1–5 years of starting muscle-building supplements.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Increasing pressure for boys to increase muscularity has led many to use muscle-building dietary supplements (MBS), which can cause many harms to include acting as a gateway to anabolic-androgenic steroid (AAS) use. This study aimed to estimate the association between MBS and initiation of AAS use.

PATIENTS: Cisgender males

INTERVENTION: Not available

CONTROL: Not available

PRIMARY OUTCOME: Prevalence of MBS over 14 years

Secondary Outcome: Initiation of AAS use within one year of using MBS

METHODS (BRIEF DESCRIPTION):

- Males 10–27 years old who participated in two Growing Up Today Studies from 1996–2004 (n=3,792) were included.
  - Participants completed six annual or biennial survey waves over 14 years (2007–2021).
  - Surveys asked about gender identity, race, and past substance use to build muscle (i.e. protein shakes, protein powders, supplements like creatine, amino acids, etc.), and AAS use.
  - 93% of participants identified as White.
  - Mean age was 20 years old at baseline with standard deviation of 3.7 years.
  - 38% of respondents reported MBS use and 0.5% reported AAS use, ever in the last year.
- AAS use was only counted once when estimating incidence even if a participant reported use across multiple waves of surveys.
- MBS use was assessed one wave of surveys prior to the initiation of AAS use in participants, with interval assessments between 1–5 years.
- Analysis was controlled for age, cohort, repeated measures, and sibling clusters.
- Odds Ratio was calculated for the prospective association between MBS use and initiation.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 14 years

RESULTS:

Primary Outcome –

- Over 14 years, the prevalence of MBS-use in the past year was 29%.
- MBS users had an eight times likelihood of starting AAS use by the next survey compared to MBS non-users (adjusted odds ratio [AOR] 8.3; 95% CI, 2.6–27).

LIMITATIONS:

- The 95% confidence interval of the odds ratio was wide.
- There were no female subjects.
- Surveys may not be the most accurate way of gathering data as participants may not understand what an MBS or AAS are, they may not remember their use over the past 1–5 years, or they may be embarrassed to answer accurately.
- Very few respondents used AAS in either the MBS user or MBS non-user groups which may overestimate the risk of MBS use in leading to AAS use.

Scott Hines, DO
David Grant Medical Center Travis AFB FMR
Fairfield, CA

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Kicking Osteoarthritis: Metformin and OA-Related Knee Pain

Metformin for Knee Osteoarthritis in Patients with Overweight or Obesity: A Randomized Clinical Trial

Pan F, Wang Y, Lim YZ, et al. Metformin for Knee Osteoarthritis in Patients with Overweight or Obesity: A Randomized Clinical Trial. *JAMA*. 2025;333(20):1804-1812. doi:10.1001/jama.2025.3471

KEY TAKEAWAY: Daily metformin does not improve knee pain at three months, but significantly improves pain at six months in adults with chronic knee pain due to osteoarthritis (OA).

STUDY DESIGN: Community-based, placebo controlled, double-blinded randomized controlled trial

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

BRIEF BACKGROUND INFORMATION: OA is a common age-related disease that can cause significant musculoskeletal pain. Due to the progressive nature of OA, with most non-invasive interventions focused on managing symptoms, discovering novel therapies is important for improving quality of life. Early research has shown that metformin may reduce inflammation and prevent cartilage degeneration, which may make it a viable treatment option for patients with OA.

PATIENTS: Adults with chronic knee pain due to OA

INTERVENTION: Metformin

CONTROL: Placebo

PRIMARY OUTCOME: Pain, stiffness, and function; quality of life

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from the greater Melbourne, Victoria, Australia area and were self-referred.
- Adults included in the study were >40 years old, body mass index (BMI) >25, with knee pain for ≥6 months and a Visual Analog Scale (VAS) score of >40. Scores on the VAS range from 40–100, with higher scores indicating worse pain.
- Patients with severe radiographic or symptomatic evidence of OA, significant knee injury, inflammatory arthritis, recent or planned surgery/injections, diabetes requiring glucose-lowering therapy, kidney impairment, or those with lower limb dysfunction were excluded from the study.
- Study was double-blinded, and patients were randomized 1:1 to metformin or placebo.
  - Patients receiving metformin started on low dose therapy and increased to 2,000 mg daily as tolerated. Therapy continued for six months.
  - Patients receiving placebo followed an equivalent medication protocol.
- Knee pain was measured using the VAS pain scale. Clinically important differences were defined as 15 points on the scale.
- Secondary outcomes were measured using the following:
  - Western Ontario and McMaster Universities Osteoarthritis Index to evaluate pain (0–500), stiffness (0–200), and function (0–1,700) before and after six months of the intervention. Higher scores in each category indicate worse pain, stiffness, and function.
  - Assessment of Quality of Life 8 Dimensions scores to assess quality of life. Scores range from 0–1, with a score of 1 indicating perfect health.

INTERVENTION (# IN THE GROUP): 54

COMPARISON (# IN THE GROUP): 53

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Metformin did not significantly reduce pain compared to placebo at three months (between-group difference –2.5; 95% CI, –12 to 6.6).
- Metformin reduced pain compared to placebo at six months (between-group difference –11; 95% CI, –20 to –2.6).

Secondary Outcome –

- Metformin improved the following compared to placebo at six months:
  - Pain (between-group difference −42; 95% CI, −84 to −1.0).
  - Stiffness (between-group difference −23; 95% CI, –40 to –5.7).
  - Function (between-group difference –180; 95% CI, –313 to –47).

- There was no significant difference in quality-of-life scores between the two groups after six months of treatment.

LIMITATIONS:

- Small sample size with 19 participants and (18%) were lost to follow-up.
- Adherence to medication may be overestimated as many participants did not return the medication at the end of the study as intended.
- Limited generalizability because of the study only included participants local to Victoria, Australia; furthermore, race and ethnicity data was not reported for the study.
- Participants were self-referred, increasing the risk of selection bias.
- Weight measurements and arthritis symptoms were all self-reported due to the study being conducted remotely.

Alexandria Lovell, MD
St Louis University School of Medicine Southwest Illinois
O'Fallon, IL