GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Family Physicians Inquiries Network

What's in this week's issue?

Week of April 25 - 29, 2022

SPOTLIGHT: Osteopathic Manipulative Treatment Combined with Exercise Improves Non-Specific Chronic Neck Pain

Osteopathic Manipulative Treatment Combined with Exercise Improves Non-Specific Chronic Neck Pain

Osteopathic manipulative treatment combined with exercise improves pain and disability in individuals with non-specific chronic neck pain: A pragmatic randomized controlled trial

Groisman S, Malysz T, de Souza da Silva L, et al. Osteopathic manipulative treatment combined with exercise improves pain and disability in individuals with non-specific chronic neck pain: A pragmatic randomized controlled trial. *J Bodyw Mov Ther.* 2020; 24(2):189–195. doi:10.1016/j.jbmt.2019.11.002

KEY TAKEAWAY: In adults with non-specific chronic neck pain (NCNP), a combination of osteopathic manipulative treatment (OMT) and exercises reduces pain and improves functional disability more than exercise alone.
STUDY DESIGN: Single-blinded, randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There are several NCNP management options including manual therapy, such as OMT and exercise, that have been shown to have clinical reductions in neck pain. However, these studies have not demonstrated the effectiveness of OMT combined with exercise.

PATIENTS: Adults with NCNP
INTERVENTION: Combination therapy of OMT with exercise (OMT/EG)
CONTROL: Exercise alone (EG)
OUTCOME: Pain severity, disability, ROM, and quality of life measures

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: 18-65 years old, neck pain for at least three months, Numeric Pain Rate Scale (NPRS) of 2 or more, Neck Disability Index (NDI) of 10 or more
- Exclusion criteria: Patients with cervical radiculopathy based on three positive results of the following: Spurling test, Distraction test, Upper Limb Tension Test A, and ipsilateral cervical rotation less than 60˚
- Comparators: Exercise Group (EG)
  - 4 weekly physical therapy led exercises (40-45 min)
  - 4 weeks of patient home exercises three times a week
- Intervention: OMT/EG
  - 4 weekly physical therapy led exercises (40-45 min)
  - 4 weeks of patient home exercises 3 times a week
  - 4 weekly full-body OMT sessions (50-60 min)
- Outcomes were collected at baseline and after four weeks of treatment.
  - NPRS: Cervical pain 11-point scale (0 = no pain, 10 = worst possible pain)
  - NDI: Disability assessment with 10-item questionnaire on 0 to 5 scale
  - Cervical Spine ROM: Cervical range of motion instrument assesses cervical mobility (range: 52–69)
  - Pressure Pain Threshold: Based on trigger point map, measures force when patient felt pain
  - Pain-self efficacy: 5 questions about patient confidence to carry out normal activities despite pain
  - Fear-Avoidance Beliefs Questionnaire (FABQ): 16-item questionnaire assessing beliefs about work and physical activity

INTERVENTION (# IN THE GROUP): 45
COMPARISON (# IN THE GROUP): 45

FOLLOW UP PERIOD: Four weeks

RESULTS:

- The OMT/EG group had improvements in pain, disability, and ROM compared with the EG group.
  - Reduction in pain on NPRS (mean difference -1.4; 95% CI -2.4 to -0.3)
  - Reduction in disability on NPI (mean difference -3.8; 95% CI, -6.9 to -0.74)
  - Increased ROM (mean difference left 6.9; 95% CI, 0.4–13 / mean difference right 8; 95% CI, 0.3–14)
- There were no significant differences between the OMT/EG group and the EG group for Pressure Pain Threshold, Pain-self efficacy, or FABQ.

LIMITATIONS:

- There was difficulty with blinding patients and osteopaths to treatment groups of OMT/EG or EG.
- Potential placebo effect from participants interacting with an osteopath in addition to OMT benefits.
- Full body OMT sessions may provide benefits other than neck pain treatment.
- There was difficulty with standardization of OMT techniques used.

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Diet and Physical Activity-Based Interventions in Antenatal Care: A Fruitful Exercise

Association of Antenatal Diet and Physical Activity-Based Interventions With Gestational Weight Gain and Pregnancy Outcomes

Teede HJ, Bailey C, Moran LJ, et al. Association of Antenatal Diet and Physical Activity-Based Interventions With Gestational Weight Gain and Pregnancy Outcomes: A Systematic Review and Meta-analysis. *JAMA Intern Med.* 2022; 182(2):106–114. doi:10.1001/jamainternmed.2021.6373

KEY TAKEAWAY: Antenatal diet and exercise interventions reduce gestational weight gain (GWG) in pregnancy.

STUDY DESIGN: Systematic review and meta-analysis of 117 RCTs (N=34,546)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high/unclear risk of bias)

BRIEF BACKGROUND INFORMATION: Excessive GWG in pregnancy is common and has been well established as an independent risk factor for adverse maternal and neonatal outcomes. Thus, obstetric providers commonly monitor GWG as a part of routine antenatal care. Previous meta-analyses have shown associations between generalized lifestyle interventions and reduced GWG, as well as adverse pregnancy outcomes.

PATIENTS: Pregnant women who receive antenatal care

INTERVENTION: Structured diet, structured physical activity, diet and physical activity with at least one structured component, or mixed

CONTROL: Routine antenatal care

OUTCOME: Mean GWG

Secondary Outcomes: Gestational diabetes, hypertensive disorders of pregnancy, pre-term delivery, cesarean delivery, fetal death, small for gestational age (SGA), large for gestational age (LGA), NICU admission

METHODS (BRIEF DESCRIPTION):

- Lifestyle interventions were classified by researchers into structured diet, structured physical activity, diet with physical activity, and mixed interventions based on specific inclusion criteria.
  - Structured diet interventions used dietary targets, with or without monitoring the supply of food.
  - Structured physical activity interventions involved specified physical activity programs conducted in controlled conditions or a few physical activity interventions that were self-led.
  - Interventions not meeting the specified criteria for structured diet or structured exercise were classified as mixed interventions.
- Data on mean GWG and maternal and neonatal outcomes were extracted for random-effects meta-analysis to generate results.

INTERVENTION (# IN THE GROUP): 29,247

COMPARISON (# IN THE GROUP): 5,299

FOLLOW UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Lifestyle interventions reduced mean GWG compared to routine care (mean difference [MD] -1.2 kg; 95% CI, -1.4 to -0.91).
- Dietary interventions (alone or with exercise) were most associated with reducing mean GWG compared to routine care.
  - Diet alone: -2.6 kg; 95% CI, -3.9 to -1.4
  - Diet and exercise: -1.4 kg; 95% CI, -2.0 to -0.75

Secondary Outcomes –

- All interventions reduced the risk of gestational diabetes compared to routine care.
  - Diet alone: OR 0.61; 95% CI, 0.45–0.8
  - Exercise alone: OR 0.60; 95% CI, 0.47–0.75
  - Diet and exercise: OR 0.64; 95% CI, 0.55–0.74
- All interventions reduced adverse maternal outcomes compared to routine care.
  - Diet alone: OR 0.75; 95% CI, 0.61–0.92
  - Exercise alone: OR 0.78; 95% CI, 0.71–0.86
  - Diet and exercise OR 0.79; 95% CI, 0.73–0.85
- Diet interventions reduced the risk of the following compared to routine care:
  - Pre-term delivery: OR 0.43; 95% CI, 0.22–0.84
  - NICU admissions: OR 0.68; 95% CI, 0.48–0.95
  - LGA: OR 0.19; 95% CI, 0.08–0.47
  - Total adverse neonatal outcomes: OR 0.44; 95% CI, 0.26–0.72
- Exercise interventions reduced the risk of the following compared to routine care:
  - HTN disorders: OR 0.66; 95% CI, 0.48–0.90
  - Cesarean delivery: OR 0.85; 95% CI, 0.75–0.95

LIMITATIONS:

- Lack of standardization among RCTs in the components and reporting of specific diet and exercise interventions.
- Variability in defining certain secondary outcomes.

- High risk of bias in 31% of studies, and unclear risk in 50%.

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The opinions and assertions contained herein are those of the authors 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, or the Department of Defense.

Getting Paid for Healthy Habits

Financial incentives for smoking cessation in pregnancy

Berlin I, Berlin N, Malecot M, Breton M, Jusot F, Goldzahl L. Financial incentives for smoking cessation in pregnancy: multicentre randomised controlled trial [published correction appears in *BMJ*. 2021 Dec 3;375:n3012] [published correction appears in *BMJ*. 2022 Feb 22;376:o448]. *BMJ*. 2021; 375:e065217. Published 2021 Dec 1. doi:10.1136/bmj-2021-065217

KEY TAKEAWAY: Financial incentives were associated with increased abstinence in pregnant people who smoke.
STUDY DESIGN: Multisite, randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Smoking during pregnancy is a modifiable risk factor that negatively impacts maternal and fetal health. Cigarette smoking is associated with low birth weight, placental insufficiency, preterm labor, and SIDS.

PATIENTS: Adults with concurrent nicotine addiction and pregnancy
INTERVENTION: Financial compensation for sustained smoking abstinence
CONTROL: Financial incentive for study visits, but no additional financial incentive for sustained abstinence
OUTCOME: Sustained smoking abstinence
Secondary Outcomes: Time to relapse, total cigarettes smoked per day, birth weight, neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- This study included 460 smokers, average age 29 years old, with an estimated gestational age of <18 weeks, who either smoked ≥5 commercial cigarettes or ≥3 hand rolled cigarettes a day.
- Participants were randomly assigned to the financial incentive group and had the opportunity to earn increasing amounts of money for sustained abstinence with a maximum earning of €520.
- The controlled group was provided with €20 vouchers for each appointment attended, but no financial incentive for abstinence with a maximum earning of €120.
- All patients received at least one 10-minute smoking cessation intervention, including motivational counselling, support, relapse prevention, and skills training at each visit.
- Monthly visits were scheduled from time of initiation and randomization (visit 1) until participants expected due date (visit 6).
- The primary outcome was sustained smoking abstinence, defined as self-report of abstinence plus expired air carbon monoxide <8 ppm, beginning from quit date selected by each participant within 15 days following visit 1 through visit 6.

INTERVENTION (# IN THE GROUP): 231
COMPARISON (# IN THE GROUP): 229

FOLLOW UP PERIOD: Six months

RESULTS:
Primary Outcome –

- Financial incentives resulted in higher smoking cessation rates (16% vs 7%, respectively; OR 2.5; 95% CI, 1.3–4.5).

Secondary Outcomes –

- Relapse occurred later in the incentivized group compared to the control group (median of visit 5 vs visit 4, respectively; *P*<.001).
- Financial incentives resulted in significantly fewer cigarettes smoked (mean difference -163; 95% CI, -302 to -23).
- There was no statistically significant difference in birth weight between the groups.
- Fewer poor neonatal outcomes occurred in the incentive group compared to the control group (4 vs 18, respectively; *P*=.0028).

LIMITATIONS:

- Abstinence was self-reported, and the expired carbon monoxide only helps to determine abstinence from the last 7 days (questionable validity of data).
- Implementation of financial incentive for smoking cessation would be difficult to implement in routine clinical care.
- Excluded patients currently being treated for psychiatric disorders, given high prevalence of comorbidity, this reduces generalizability.
- Did not collect data on effects of long-term cessation.

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COVID-19 Vaccination in Children Between 5 and 11 Years Old: Is It Worth a Shot?

Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 years of Age

Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *N Engl J Med*. 2022; 386(1):35–46. doi:10.1056/NEJMoa2116298

KEY TAKEAWAY: Two dose series of BNT162b2 10 ug 21 days apart provides safe, effective, and immunogenic response in children five to eleven years old.

STUDY DESIGN:

- Phase 1: Open-label, dose-finding study
- Phase 2: Multisite, double-blind randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The COVID-19 pandemic has interfered with the emotional, social, and mental wellbeing of children in addition to their physical wellbeing. Finding a safe and efficacious way to prevent the continued spread and development of variant forms of COVID-19 is imperative to preventing further harm to the development of children.

PATIENTS: Five to eleven year old children

INTERVENTION:

- Phase 1: BNT162b2 varied doses x2 (10 ug, 20 ug, 30 ug)
- Phase 2: BNT162b2 10 ug injection given twice 21 days apart

CONTROL:

- Phase 1: No Control
- Phase 2: Placebo injection given twice, 21 days apart

OUTCOME:

- Phase 1: Reactogenicity and immunogenicity
- Phase 2: Immunogenicity, efficacy, and safety

METHODS (BRIEF DESCRIPTION):

- Children five to eleven years old (mean 7.9 years old) without pre-existing conditions or those with stable conditions were recruited.
  - 79% White, 6% Black, 10% Asian, 8% Hispanic
- Phase 1: Dose-finding comparing 10 ug, 20 ug, 30 ug
  - Four participants in each group received their vaccination and were monitored for safety concerns for two days. If there were no concerns, all participants received their vaccination followed by a booster at 21 days.
  - Blood samples taken at seven days after the second vaccination were taken to assess immunogenicity using SARS-CoV-2 neutralization titers to measure geometric mean ratios.
- Phase 2:
  - Participants were randomly assigned in a 2:1 ratio to receive 2 doses, 21 days apart of BNT162b2 10 ug or saline placebo.
  - Serum samples from five to eleven year olds were compared to those of 16-25 year olds and assayed in parallel for titer comparability and seroresponse was compared between age groups using geometric mean titers (GMTs).
    - Seroresponse was defined as a 4-fold increase in titers from baseline or 4 times the lower limit of normal if baseline was less than the lower limit of quantitation.
  - Safety was evaluated with an electronic diary for one month after second dose, with plans to follow for six months.
- Efficacy was assessed by COVID-19 onset at least seven days after the second vaccination and seroresponse.

INTERVENTION (# IN THE GROUP):

- Phase 1: 48
- Phase 2: 1,518

COMPARISON (# IN THE GROUP):

- Phase 1: Not applicable
- Phase 2: 750

FOLLOW UP PERIOD:

- Phase 1: Seven days
- Phase 2: Six months

RESULTS:

Primary Outcome –

- 10 ug provided safe and adequate immune response with neutralizing GMTs of 4,163 vs 4,583 with the 20 ug dose in phase I.
- Safety: BNT162b2 recipients reported more local reactions and systemic events than placebo recipients. No serious adverse events were noted.
  - Local reactions included injection site pain, redness, and swelling.
  - Systemic events included primarily fatigue, headache, and fever.
- Immunogenicity: There was no significant difference between GMT of five to eleven year olds receiving 10

ug dose and 16-25y/o receiving 30 ug dose (geometric mean ratio 1.0; 95% CI, 0.9–1.2).
- Efficacy: The vaccine was 91% effective (95% CI, 68–98).

LIMITATIONS:

- The study was not powered to detect potential rare side effects.
- There was no assessment of BNT162b2 with concomitant administration of other vaccines.
- The study population race breakdown does not reflect the general population with a greater proportion in the study being white resulting in lack of generalizability.
- Funding was provided by the vaccine company.
- Study had relatively short follow up resulting in long term immunogenicity, safety, and clinical efficacy not being assessed.

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Is Amplatzer Amulet Left Atrial Appendage Occluder Superior to Watchman Device for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation?

Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE)

Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE): A Randomized, Controlled Trial. *Circulation*. 2021; 144(19):1543–1552. doi:10.1161/CIRCULATIONAHA.121.057063

KEY TAKEAWAY: Compared with the Watchman Device (WD), Left Atrial Appendage Occlusion (LAAO) with a dual-seal mechanism using the Amplatzer Amulet (AA) was noninferior with superior occlusion rates.

STUDY DESIGN: Randomized, multicenter, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with nonvalvular atrial fibrillation are at increased risk of ischemic stroke due to stagnation of blood in the left atrial appendage (LAA) promoting thrombus formation. The single-seal mechanism WD was approved for LAAO. However, LAAO with a single-seal mechanism may be incomplete because of the complex and variable anatomy of the LAA. The AA uses a dual-seal technique with hopes of achieving better occlusion. Previously, no randomized, multicenter trials comparing different devices with clinical outcome assessment had been performed.

PATIENTS: Adults with documented paroxysmal, persistent, or permanent nonvalvular atrial fibrillation.

INTERVENTION: Amplatzer Amulet (AA)

CONTROL: Watchman Device (WD)

OUTCOME: Safety and effectiveness composites, LAA occlusion

METHODS (BRIEF DESCRIPTION):

- Patients were adults, (average age 75 years old) with documented paroxysmal, persistent, or permanent nonvalvular atrial fibrillation with CHADS2 score ≥2 or CHA2DS2-VASc score of ≥3. LAA anatomy was assessed with TEE.
- Patients were also screened for an extensive exclusion criterion which included class IV heart failure, recent heart attack within 90 days, a left ventricular ejection fraction of <30%, mechanical valve prosthesis, thrombocytopenia or anemia requiring transfusion, severe renal failure, or life expectancy <2 years.
- Patients were randomly assigned.
- Patients were evaluated at 45 days to assess the rate of LAAO.
- Safety endpoints (procedure-related complications, all-cause death, or major bleeding) were evaluated at 12 months.
- Effectiveness endpoints (ischemic stroke or systemic embolism) were evaluated at 18 months.

INTERVENTION (# IN THE GROUP): 903

COMPARISON (# IN THE GROUP): 885

FOLLOW UP PERIOD: 18 months

RESULTS:

- The AA was noninferior but not superior to the WD in terms of:
  - Safety (15% vs 15%; HR –0.14; 95% CI, –3.4 to 3.1; *P*<0.001 for noninferiority; *P*=0.47 for superiority)
  - Effectiveness (2.8% vs. 2.8%; HR 0.00; 95% CI, –1.6 to 1.6; *P*<0.001 for noninferiority, *P*=0.50 for superiority)
  - Successful LAAO (99% vs 97%; HR 2.0; 95% CI, 0.41–3.7; *P*<0.001 for noninferiority, *P*=0.003 for superiority)

LIMITATIONS:

- The study had many exclusion criteria which limits the generalizability of the findings.
- Echo lab was not blinded.
- The study used the first-generation Watchman Device and not the newer one.
- Different antithrombotic regimens may affect outcomes.

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