GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 16- 20, 2024

SPOTLIGHT:

Exercise Intensity and Modality Matter in the Treatment of Depression

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Exercise Intensity and Modality Matter in the Treatment of Depression

Effect of Exercise for Depression: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Noetel M, Sanders T, Gallardo-Gómez D, et al. Effect of exercise for depression: systematic review and network meta-analysis of randomized controlled trials [published correction appears in BMJ. 2024 May 28;385:q1024. doi: 10.1136/bmj.q1024]. *BMJ*. 2024;384:e075847. Published 2024 Feb 14. doi:10.1136/bmj-2023-075847

KEY TAKEAWAY: Exercise improves symptoms of depression with results directly proportional to intensity. Walking or jogging, strength training, and yoga are more effective than other exercise modalities.

STUDY DESIGN: Systematic review and network meta-analysis of 218 randomized controlled trials (RCTs) (N=14,170)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Major depressive disorder (MDD) affects people from all walks of life and backgrounds. It can exacerbate comorbidities such as cancer and heart disease and is a factor in thousands of suicides in the United States each year. Drug treatments such as selective serotonin reuptake inhibitors (SSRIs) and psychotherapy can be effective. However, many people suffer from being resistant to these treatments. Exercise can be recommended as an adjunct or an alternative treatment when treating MDD however, recommendations for modalities and intensities vary among practitioners. This study aimed to investigate which modalities of exercise are most effective in the role of an adjunct or alternative treatment for depression, and if different intensities of such exercises are better than others for this treatment.

PATIENTS: Participants with MDD

INTERVENTION: Various exercise types and intensity

CONTROL: SSRIs and/or psychotherapy, standard care, placebo

PRIMARY OUTCOME: Depressive symptom improvement

METHODS (BRIEF DESCRIPTION):

- Included studies were RCTs with participants suffering from MDD and exercise as a treatment.
- Individuals meeting the clinical threshold of the DSM-5 definition of MDD were included in the study.
- Modes of exercise included jogging or walking, yoga, cycling, strength training, tai chi or qigong, dance, aerobic exercise, and relaxation.
    - Metabolic equivalents of task (METs) were calculated for each arm of studies included using Compendium of Physical Activities to rank intensity.
    - For each intervention modality METs were calculated based on frequency, intensity, and type.
- Standard care, placebo, educational control, and social support were included as study controls.
- Pre-test depression scores were compared to post-test depression scores to measure the primary outcome of the study.
    - A variety of scales were used to assess symptoms of depression in the included RCTs using the National Institute for Health (NIH) and Care Excellence guidelines.
    - Using an internal reference standard for each scale such as the average of pooled standard deviations allowed these scores to be compared from different studies.
- Standardized change scores for improvement of symptoms were calculated using a Hedges' g value where the more negative the value, the greater the benefit. The clinically important benefits begin at –0.2.
- The credible interval represents the range of repetition to reoccur 95% of the time.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Dance resulted in a large reduction of depressive symptoms compared to active controls (5 studies, n=107; mean change –0.96; 95% credible interval, –1.4 to –0.56).
- Walking or jogging, yoga, strength training, mixed aerobic exercise, and tai chi or qigong resulted in a

moderate reduction in depressive symptoms compared to active controls:

- Walking or jogging (51 studies, n= 1,210; mean change –0.63; 95% credible interval, –0.80 to –0.46)
- Yoga (33 studies, n=1,210; mean change –0.55; 95% credible interval, –0.73 to –0.36)
- Strength training (22 studies, n=643; mean change –0.49; 95% credible interval, –0.69 to –0.29)
- Mixed aerobic exercise (51 studies, n=1,286; mean change –0.43; 95% credible interval, –0.61 to –0.25)
- Tai chi or qigong (12 studies, n=343; mean change –0.42; 95% credible interval, –0.65 to –0.21)

- The dose-response curve for the intensity of exercise prescribed showed an expected effect that was stronger for vigorous exercise (mean change –0.74; 95% credible interval, –1.1 to –0.38).

LIMITATIONS:

- Some modalities such as dance had a small number of participants included.
- Blinding was difficult for these types of treatments.
- Many studies were focused on specific sub-populations, so the modality was tailored to these populations, which may result in confounding.

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Mild-to-Moderate and Moderate-to-Severe Acne Vulgaris: What Really Works?

A Systematic Review and Network Meta-Analysis of Topical Pharmacological, Oral Pharmacological, Physical and Combined Treatments for Acne Vulgaris

Mavranezouli I, Daly CH, Welton NJ, et al. A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. *Br J Dermatol*. 2022;187(5):639-649. doi:10.1111/bjd.21739

KEY TAKEAWAY: Topical treatment combinations, chemical peels, and photochemical therapy are more effective than placebo for mild-to-moderate acne. Topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin, and photodynamic therapy are more effective for moderate-to-severe acne compared to monotherapies.

STUDY DESIGN: Systematic review and network meta-analysis of 179 randomized controlled trials (RCTs) (N=approximately 35,000 observations)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Acne vulgaris is a highly prevalent skin condition affecting millions worldwide. The effectiveness of available treatments varies, and there is considerable uncertainty regarding their comparative efficacy, particularly across different severities of acne. This study aimed to evaluate the relative effectiveness of topical, oral, physical, and combination therapies for mild-to-moderate and moderate-to-severe acne.

PATIENTS: Patients with acne vulgaris

INTERVENTION: Topical, oral, physical, or combined treatments

CONTROL: Placebo

PRIMARY OUTCOME: Efficacy

Secondary Outcome: Tolerability

METHODS (BRIEF DESCRIPTION):

- Included patients were all ages with mild-to-moderate and moderate-to-severe acne vulgaris.
- Neonatal acne, post-inflammatory dyspigmentation, polycystic ovary syndrome (PCOS), and those receiving maintenance treatment or refractory acne were excluded from the study.
- Treatments were categorized into groups:
  - Topical treatments included retinoids, antibiotics, benzoyl peroxide (BPO), and azelaic acid.
  - Oral treatments included antibiotics, isotretinoin, hormonal contraceptives, and hormone-modifying agents such as metformin and spironolactone.
  - Physical treatments included chemical peels (salicylic acid, mandelic acid, and Jessner's peel), photochemical therapy (blue/red light), and photodynamic therapies (light therapy enhanced by a photosensitizing chemical).
  - Combined treatments included combinations of the above modalities within and across treatment classes.
- All control groups (topical vehicles, oral placebos, physical sham placebos) were included under a broader placebo control class.
- Efficacy was primarily assessed using clinician-rated improvement after inter-rater reliability determination.
- Acne severity scales were used, where applicable, with higher scores indicating greater severity and lower scores indicating improvement.

INTERVENTION (# IN THE GROUP): 26,869

- Mild-to-moderate acne:
  - Topical: 10,438
  - Oral: 3,482
  - Physical: 457
  - Combined: 146
- Moderate-to-severe acne:
  - Topical: 8,298
  - Oral: 2,518
  - Physical: 139
  - Combined: 1,391

COMPARISON (# IN THE GROUP): 12,995

- Mild-to-moderate acne:
  - Placebo: 4,703
  - No treatment: 39
- Moderate-to-severe acne:
  - Placebo: 8,228
  - No treatment: 25

FOLLOW-UP PERIOD: Varied (0–24 weeks)

RESULTS:

Primary Outcome –

- For treating mild-to-moderate acne, the most effective options in each category were:
  - A combination of topical retinoids and topical BPO was more effective in the treatment of acne vulgaris compared to placebo (n=1,057; mean difference [MD] 26%; 95% credible interval, 17–35).
  - Chemical peels were more effective in the treatment of acne vulgaris compared to placebo (n=101; MD 40%; 95% credible interval, 12–66).
  - Photochemical therapy was more effective in the treatment of acne vulgaris compared to placebo (n=69; MD 35%; 95% credible interval, 17–53).
- For treating moderate-to-severe acne, the most effective treatments in each category were:
  - A combination of topical retinoid with topical clindamycin was more effective in the treatment of acne vulgaris compared to placebo (n=1,548; MD 44%; 95% credible interval, 29–60).
  - Oral isotretinoin, with a total cumulative dose of ≥120 mg/kg^{-1} per course, was more effective in the treatment of acne vulgaris compared to placebo (n=182; MD 58%; 95% credible interval, 36–79).
  - Photodynamic therapy was more effective in the treatment of acne vulgaris compared to placebo (n=298; MD 40%; 95% credible interval, 26–54).
  - A combination of BPO, with topical retinoid and oral clindamycin, was more effective in the treatment of acne vulgaris compared to placebo (n=556; MD 45%; 95% credible interval, 29–58).

Secondary Outcome –

- For mild-to-moderate acne, the tolerance of topical retinoids and BPO was lower compared to the placebo (n=957; log odds ratio [LOR] 1.5; 95% credible interval, 0.69–2.3).
- For moderate-to-severe acne, the tolerance of topical retinoids and oral tetracyclines was lower compared to placebo (n=379; LOR 2.1; 95% credible interval, 0.14–4.3).

LIMITATIONS:

- The search included only studies published in English.
- Only treatments included are used in the United Kingdom (UK), limiting effective drug treatments.
- The included RCTs were moderate to very low quality, introducing potential bias and uncertainty into the findings.
- Inconsistencies between direct and indirect evidence estimates were observed, potentially due to variations in populations (such as age or acne severity definitions), treatment regimens, or study designs (parallel vs split-face) across the included RCTs.

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Does Azithromycin Prevent Asthma When Given During Acute RSV Bronchiolitis?

Azithromycin to Prevent Recurrent Wheeze Following Severe Respiratory Syncytial Virus Bronchiolitis

Beigelman A, Srinivasan M, Goss CW, et al. Azithromycin to Prevent Recurrent Wheeze Following Severe Respiratory Syncytial Virus Bronchiolitis. *NEJM Evid*. 2022;1(4):10.1056/evidoa2100069. doi:10.1056/evidoa2100069

KEY TAKEAWAY: Azithromycin does not improve recurrent wheezing compared to placebo administration during a severe respiratory syncytial virus (RSV) bronchiolitis episode.

STUDY DESIGN: Randomized, single-center, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previous RSV infection is a risk factor for the future development of asthma according to current statistical data. Azithromycin is known to be of benefit in some neutrophil-derived inflammatory states. This study hypothesized that by decreasing the amount of inflammation during a bronchiolitis episode, the increased risk of post-RSV wheezing development may be mitigated.

PATIENTS: Children with severe RSV bronchiolitis

INTERVENTION: Azithromycin

CONTROL: Placebo

PRIMARY OUTCOME: Recurrent wheezing

Secondary Outcome: Annualized number of days with any respiratory symptoms, days with albuterol use, number of oral glucocorticoid courses, number of antibiotic courses, asthma diagnosis

METHODS (BRIEF DESCRIPTION):

- Previously healthy children 1–18 months old with severe RSV bronchiolitis were included in the study
- Severe RSV bronchiolitis was defined as having two of the following: Tachypnea with respirations >40, wheezing, cough, auscultation of rales, crackles, and/or rhonchi on an exam, or retractions.
- Patients were blinded and randomized to one of the following treatments:
  - Oral azithromycin 10 mg/kg daily for seven days, followed by 5 mg/kg daily for seven days
  - Placebo for the same duration
- Providers were blinded to treatments.
- The primary outcome measured recurrent wheezing as assessed by the patient's parents. A new wheezing episode was defined if ≥7 days without wheezing had been reported since the previous episode.
- The secondary outcomes measured the annualized number of days with any respiratory symptoms, days with albuterol use, number of oral glucocorticoid courses, number of antibiotic courses, and asthma diagnosis.
- Participants were assessed in the clinic every six, 18, 30, and/or 42 months (except for in 2020 during the COVID-19 pandemic). Patients were also followed via telephone interviews every two months.

INTERVENTION (# IN THE GROUP): 96

COMPARISON (# IN THE GROUP): 92

FOLLOW-UP PERIOD: Varied (2–4 years)

RESULTS:

Primary Outcome –

- Administration of azithromycin did not affect the risk of recurrent wheezing compared to placebo (unadjusted hazard ratio [HR] 1.5; 95% CI, 0.95–2.3).

Secondary Outcome –

- No differences were found between the azithromycin and placebo groups in the diagnoses of asthma, the annualized number of days with any respiratory symptoms, days with albuterol use, the number of oral glucocorticoid courses, and the number of antibiotic courses.

LIMITATIONS:

- The primary outcome was recurrent wheeze assessed by parents, which the researchers point out, has not been shown to correlate well with wheeze assessed by physicians.
- The last year of the study was affected by the COVID-19 pandemic, and the researchers noticed fewer wheezing episodes in both treatment arms during that time frame. They attributed this to social distancing, lower prevalence of most viral infections, and lower levels of air pollution.
- Additionally, the one in-person visit with participants was changed to another phone interview in the last year of the study.

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Effects of Weight Loss in Older Adults with Obesity on Insulin Sensitivity

Weight Loss and Exercise Differentially Affect Insulin Sensitivity, Body Composition, Cardiorespiratory Fitness, and Muscle Strength in Older Adults with Obesity: A Randomized Controlled Trial

Brennan AM, Standley RA, Anthony SJ, et al. Weight Loss and Exercise Differentially Affect Insulin Sensitivity, Body Composition, Cardiorespiratory Fitness, and Muscle Strength in Older Adults With Obesity: A Randomized Controlled Trial. *J Gerontol A Biol Sci Med Sci*. 2022;77(5):1088-1097. doi:10.1093/gerona/glab240

KEY TAKEAWAY: Exercise with calorie-restriction-induced weight loss increases insulin sensitivity compared to health education alone in older adults with obesity.

STUDY DESIGN: Randomized, controlled trial with parallel group design

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic disease risk, including cardiovascular disease, diabetes, obstructive sleep apnea (OSA), and debility, increases with age, obesity, and physical inactivity. Current physical activity guidelines include specific durations of activity and intensities, but no specific detail of the provided benefits is indicated or well-known among the average population. There are also numerous methods of weight loss being presented to the public, many of which are falsely advertised and ineffective with potential harmful risks. This study examined the physical and physiologic benefits of weight loss and which method of weight loss is most advantageous using current standards of care in utilizing exercise and caloric restriction.

PATIENTS: Physically inactive older obese adults

INTERVENTION: Calorie restriction-induced weight loss (WL) or calorie restriction weight loss with exercise (WLEX)

CONTROL: Health education alone (HEC)

PRIMARY OUTCOME: Insulin sensitivity

Secondary Outcome: Blood analyses, cardiorespiratory fitness, strength, functional performance, body composition

METHODS (BRIEF DESCRIPTION):

- Men and women 60–80 years old who were physically inactive (≤1 continuous exercise session/week), obese (BMI >30), nonsmokers, and had a blood pressure <150/95 were included in the study.
- Individuals with clinically significant cardiovascular disease, including a history of myocardial infarction (MI) within the past year, peripheral vascular disease, hepatic, renal, muscular/neuromuscular, or active hematologic/oncologic disease, presence of bruits in the lower extremities, history of pulmonary emboli (PE), peripheral neuropathy, anemia, and substance abuse were excluded from the study.
- Medications excluded included anticoagulants, glucocorticoids, thiazolidinediones, and insulin.
- Patients were blinded and randomized to one of the following treatments:
  - Calorie restriction-induced (WL) to lose 10% bodyweight involved 500–1,000 kcal/d restriction adjusted with the Harris-Benedict equation.
  - Calorie restriction (WLEX) involved 4–5 days per week, 45-minute sessions consisting of walking, with the option of stationary cycling, elliptical, and/or rowing machines. Progression to adding resistance training began at week eight.
- Treatments were administered by registered dieticians and trained monitors supervising exercise.
- The health education comparison (HEC) group underwent twice-weekly education seminars on medications and management of type 2 diabetes (T2DM). The participants in this group did not receive dietary or exercise education.
- Insulin sensitivity was measured as the primary outcome using a hyperinsulinemic-euglycemic clamp. It was executed 36–48 hours after the last exercise in the intervention group.
- The following were measured as the primary outcomes:
  - Blood analyses were assessed using lipid profiles and hemoglobin A1C (HgA1c) measurements.
  - Cardiorespiratory fitness, strength, and functional performance were assessed via maximal oxygen uptake (VO_{2peak}) by a cardiopulmonary graded exercise test administered by an exercise physiologist, a Short Physical Performance Battery used to

measure lower extremity functional capacity. Strength and power were assessed at baseline and six months using a pneumatic-driven dynamometer (Biodex).
    - Body composition, including weight loss and waist circumference, was measured using dual-energy X-ray absorptiometry to estimate fat mass and fat-free mass and magnetic resonance imaging (MRI) to assess abdominal/thigh muscle volume and adipose tissue.

INTERVENTION (# IN THE GROUP):

- WL: 31
- WLEX: 28

COMPARISON (# IN THE GROUP): 25

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- WLEX increased skeletal muscle insulin sensitivity compared to HEC (0.05 vs 0.0 mL/kgFFM/min/insulin, respectively; $p<.05$).

Secondary Outcome –

- There was no significant difference in lipid profiles between WLEX and WL groups.
- WLEX significantly improved fasting insulin compared to both WL and HEC (–5.5 vs –4.3 and –2.0 mg/dL; $p=.02$).
- WLEX significantly improved HbA1c values compared to both WL and HEC (–0.6% vs –0.2% and –0.1%; $p<.01$).
- The WLEX group had a higher maximal VO_{2peak} compared to both WL and HEC (2.6 vs –1.2 and –1.4 mL/kgFFM/min; $p<.05$).
- There was no statistical difference in functional performance between any intervention group.
- WLEX resulted in more weight loss compared to WL (–11% vs –7.1%, respectively; $p<.05$).
- WLEX reduced waist circumference compared to HEC (–8.7 vs –2.3 cm, respectively; $p=.01$).
- WLEX reduced fat mass compared to both WL and HEC (–8.6 vs –5.0 and –1.4 kg; $p<.0001$).
- WLEX reduced abdominal fat compared to HEC (–2.2 vs –0.5 kg, respectively; $p<.05$).
- WLEX reduced visceral fat compared to HEC (–1.4 vs –0.1 kg, respectively; $p<.05$).

LIMITATIONS:

- The patient population was strictly older obese inactive adults.
- Minimal ethnic diversity.
- No reported socioeconomic diversity.
- A relatively small patient population was studied.

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Easing the Pain: Does Scheduled Ketorolac Reduce Opioid Use Post-Cesarean Section?

Increased Scheduled Intravenous Ketorolac After Cesarean Delivery and Its Effect on Opioid Use: A Randomized Controlled Trial

Hostage J, Kolettis D, Sverdlov D, et al. Increased Scheduled Intravenous Ketorolac After Cesarean Delivery and Its Effect on Opioid Use: A Randomized Controlled Trial. *Obstet Gynecol*. 2023;141(4):783-790. doi:10.1097/AOG.0000000000005120

KEY TAKEAWAY: In postpartum patients after cesarean-section (CS), scheduled ketorolac, compared to placebo, reduces opioid use.

STUDY DESIGN: Randomized, placebo-controlled, double-blinded study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to significant dropout rate and small sample size)

BRIEF BACKGROUND INFORMATION: A significant portion of people who deliver by CS receive postpartum opioids for post-operative pain, and a percentage of these become prolonged opioid courses. Given the risks associated with prolonged use of post-operative opioids, other ways to control postpartum pain are important to study. Few studies directly compare non-opioid and opioid medications for pain control post-CS. This study aimed to determine the efficacy and safety of intravenous (IV) NSAIDs in reducing post-operative opioid use.

PATIENTS: Patients post-CS

INTERVENTION: IV ketorolac

CONTROL: IV saline

PRIMARY OUTCOME: Opioid use in morphine milligram equivalents (MME)

Secondary Outcome: Laboratory data and subjective evaluations of pain control and overall satisfaction

METHODS (BRIEF DESCRIPTION):

- This was a randomized, double-blind, placebo-controlled parallel-group clinical trial conducted at a single center.
- Patients ≥16 years old and delivered via CS under neuraxial analgesia and who did not have any of the exclusion criteria, including allergy to non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcer disease (PUD), previous kidney/liver disease, gestational or chronic hypertension (HTN), pre-eclampsia, HELLP syndrome, eclampsia, or bleeding/clotting disorders were included in the study.
- The patients' mean age was 33 years old, and their mean gestational age was 38 weeks. There were no differences in BMI (mean 31 kg/m^2) or other baseline characteristics.
  - In the placebo group, 43% of participants self-reported their race as White, 20% as Black, and 5.4% as Asian.
  - In the ketorolac group, 50% self-reported their race as White, 11% as Black, and 8.1% as Asian.
- All patients received scheduled ketorolac 30 mg IV for initial two doses post-operatively.
  - 12 hours after the first dose, patients received either continued scheduled ketorolac or saline IV every six hours for four doses by random assignment by the hospital's investigational pharmacy.
- Patients also had access to acetaminophen and oxycodone, but all other NSAIDs were held in both groups until six hours after the last study drug dose.
- Cumulative MMEs were calculated based on opioid pain medication received while inpatient until 72 hours post-operative or hospital discharge, whichever occurred first.
- Blood was collected to evaluate hematocrit on post-operative days zero and one, and to evaluate creatinine on post-operative days one and two.
- Postpartum pain scores were evaluated per routine institutional policy by nursing staff, on a 0–10 scale with higher scores indicative of worse pain.
  - Patients with scores >3 were included in the statistical analysis.
- Satisfaction with postpartum experience and pain control was determined by a postpartum telephone call two weeks postpartum, assessed on a five-point scale. Lower scores indicated worse satisfaction.
- All study data was collected by research staff who were blinded to the participant's study group.

INTERVENTION (# IN THE GROUP): 74

COMPARISON (# IN THE GROUP): 74

FOLLOW-UP PERIOD: Two weeks

RESULTS:

Primary Outcome –

- Scheduled ketorolac significantly reduced median cumulative MME compared to placebo at 72 hours (median difference [MD] –30; 95% CI, –45 to –15).

Secondary Outcome –

- The use of ketorolac reduced the percentage of patients reporting pain scores >3 compared to placebo (results presented via figure; *p*=.005), driven by statistically significant differences at 30 and 36-hour time points.
- There was no significant difference in baseline hematocrit or the change in creatinine from baseline to post-operative day one or post-operative day two.
- There was no significant difference in postpartum satisfaction with care and report of pain control.

LIMITATIONS:

- This study had a small sample size, though was adequately powered to show a 30% reduction in MME.
- The placebo group was not allowed any oral NSAIDs, so efficacy cannot be compared to this commonly used alternative.
- Only 59 patients (82%) in the placebo group and 60 patients (85%) in the ketorolac group received all four doses of the study drug, with loss of IV access being the most common reason for protocol deviations.
- Only about 60% of both arms completed the postpartum telephone call.
- A pause in recruitment occurred during the Spring of 2020 due to restrictions related to the COVID-19 pandemic.

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Using Osteopathic Manipulation for the Treatment of Major Depressive Disorder

Effectiveness of Osteopathic Manipulative Applications on Hypothalamic-Pituitary-Adrenal (HPA) Axis in Youth with Major Depressive Disorder: A Randomized Double-Blind, Placebo-Controlled Trial

Pala ÖO, Çıtaker S, Güney E, et al. Effectiveness of osteopathic manipulative applications on hypothalamic-pituitary-adrenal (HPA) axis in youth with major depressive disorder: a randomized double-blind, placebo-controlled trial. *J Osteopath Med*. 2024;124(6):267-275. Published 2024 Feb 29. doi:10.1515/jom-2023-0056

KEY TAKEAWAY: Osteopathic sympathetic harmonization (OSH) application in youth with major depressive disorder (MDD) does not improve anxiety levels compared to placebo.

STUDY DESIGN: Double-blind, placebo-controlled, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and placebo not being a true placebo)

BRIEF BACKGROUND INFORMATION: Youth with depression are less likely to be appropriately diagnosed and treated compared to adults. Depression and other stressors can cause activation of the sympathetic neural axis involving the hypothalamic-pituitary axis (HPA) axis which can be assessed with cortisol levels. Additionally, stressors can activate the sympathetic adrenal axis which can be assessed with amylase levels. These processes are ways that the body can respond to stressors. This study sought to determine whether the effects of osteopathic manipulation techniques targeting the sympathetic nervous system (SNS) and HPA axis can lead to improvement in youth patients with MDD.

PATIENTS: Youth diagnosed with MDD

INTERVENTION: OSH

CONTROL: Placebo

PRIMARY OUTCOME: Anxiety

Secondary Outcome: Blood pressure (BP), heart rate (HR), a-amylase levels, cortisol levels

METHODS (BRIEF DESCRIPTION):

- 39 youth patients 15–21 years old diagnosed with MDD per DSM-5 criteria were included in the study.
- Participants were randomized into either the OSH group or placebo group based on participant sex with the first case for each sex determined by a coin flip.
- OSH group underwent stimulation of prevertebral ganglia and paravertebral ganglia.
- The placebo group underwent stimulation with a light touch, shorter pushes, and lateral to similar locations.
- Beck Depression Inventory (BDI) and the State and Trait Anxiety Inventory (SAI and TAI) were administered to all participants before the application of OSH or placebo.
    - The BDI screens for depression. Scores range from 0–63 with low scores indicating minimal depression and higher scores indicating severe depression.
    - The SAI and TAI measures anxiety. Scores range from 20–80 with lower scores indicating minimal anxiety and higher scores indicating severe anxiety.
    - The two groups had similar levels of anxiety and depression at baseline.
- The primary outcome measured anxiety using the State Anxiety Inventory (SAI).
- Saliva samples, blood pressure, and pulse measurements were taken before, immediately after, and 20 minutes after stimulation application to determine cortisol and a-amylase levels in the participants.

INTERVENTION (# IN THE GROUP): 19

COMPARISON (# IN THE GROUP): 20

FOLLOW-UP PERIOD: 20 minutes

RESULTS:

Primary Outcome –

- OSH did not improve anxiety compared to the placebo group at 20 minutes (mean 40 vs 45, respectively; *p*=.22).

Secondary Outcome –

- There was no statistically significant difference in HR, systolic BP, and diastolic BP in the OSH compared to the placebo group before, immediately after, and at 20 minutes after application.
- OSH decreased a-amylase levels compared to the placebo group at 20 minutes (mean 280 vs 324 u/L, respectively; *p*=.028).

- OSH increased cortisol levels compared to the placebo group at 20 minutes (mean 2.2 vs 1.9 ng/mL, respectively; *p*=.009).

LIMITATIONS:

- The placebo group still received minimal stimulation compared to no stimulation and thus receptors sensitive to touch and pressure will still be stimulated which results in the same input to the cortex of both OSH and placebo groups.
- The sympathetic chain may be affected by any intervention to the ribs regardless of whether there was direct stimulation in the OSH group or more laterally in the placebo group.
- The study did not follow patients longitudinally and thus there is no information on the effects past 20 minutes post application or the effect of multiple sessions of OSH.
- Participants with a history of OSH were not excluded. Thus, if participants with previous OSH experience were in the placebo group, they may have a bias to know how effective OSH is to be administered.
- A small sample size with 19 participants in the intervention group and 20 participants in the control group, may cause a lack of generalizability.

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More Steps a Day: Take Your Cardiac Disease Risk Away

Do the Association of Daily Steps with Mortality and Incident Cardiovascular Disease Differ by Sedentary Time Levels? A Device-Based Cohort Study

Ahmadi MN, Rezende LFM, Ferrari G, Del Pozo Cruz B, Lee IM, Stamatakis E. Do the associations of daily steps with mortality and incident cardiovascular disease differ by sedentary time levels? A device-based cohort study. *Br J Sports Med*. 2024;58(5):261-268. Published 2024 Mar 8. doi:10.1136/bjsports-2023-107221

KEY TAKEAWAY: Participants with both low and high sedentary time who obtain >2,200 steps per day are at a lower risk for all-cause mortality and cardiovascular disease (CVD) compared to individuals achieving ≤2,200 steps per day. The optimal number of steps to reduce CVD and lower risk for all-cause mortality ranged from 9,000–10,300 depending upon sedentary status.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Evidence has shown that healthcare providers prescribe increasing daily steps to reduce morbidity and mortality.
High sedentary time is associated with an increased risk of morbidity and mortality. This study aimed to investigate the effect of daily steps in patients with high and low sedentary times.

PATIENTS: Participants 40–69 years old willing to wear an accelerometer

INTERVENTION: Sedentary time and daily step count

CONTROL: ≤2,200 daily steps

PRIMARY OUTCOME: All-cause mortality and incident CVD

METHODS (BRIEF DESCRIPTION):

- Data was obtained through the UK biobank study.
- Participants with diagnosed CVD and cancer were excluded from the study.
- Daily step count and sedentary time were measured using the Axivity AX3 accelerometer. Patients wore it on their wrist for 24 hours per day for seven days.
  - Low sedentary time was defined as <10.5 hours per day.
  - High sedentary time was defined as ≥10.5 hours per day.
- The reference point was 2,200 steps per day.
- A day was counted if the participant wore the accelerometer ≥16 hours per day.
- Patients were required to have at least three monitoring days per week with one being a weekend day.
- All-cause mortality was measured as the primary outcome and was determined as deaths obtained through linkage with the NHS Digital of England and Wales or the NHS Central Register and National Records of Scotland.
  - Cox proportional hazard regression models were used to estimate hazard ratios.
- Incident CVD was measured as the second primary outcome and was defined as diseases of the circulatory system, excluding hypertension, diseases of arteries, and the lymphatic system.
  - Fine-Gray sub-distribution method was used for incident CVD analyses with non-cardiovascular deaths treated as a competing risk.

INTERVENTION (# IN THE GROUP): 38,836

COMPARISON (# IN THE GROUP): 33,338

FOLLOW-UP PERIOD: 6.9 years

RESULTS:

Primary Outcome –

- In highly sedentary individuals, the optimal number of steps to reduce all-cause mortality is 9,000 steps (hazard ratio [HR] 0.61; 95% CI, 0.51–0.73).
- In highly sedentary individuals the optimal number of steps to reduce CVD is 9,700 steps (HR 0.79; 95% CI, 0,72–0.86).
- In low-sedentary individuals, the optimal number of steps to reduce all-cause mortality is 10,300 steps (HR 0.69; 95% CI, 0.52–0.92).
- In low-sedentary individuals, the optimal number of steps to reduce CVD is 9,800 steps (HR 0.61; 95% CI, 0.61–0.83).

LIMITATIONS:

- Patients with diagnosed CVD and cancer were excluded.
- The observational design allows for the presence of unmeasured confounding variables.
- Most of the participants were White (96%), which limits the applicability to the general population.

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