GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Pinpointing the Most Effective Treatment for Acne Vulgaris

- Wellness is an Active Lifestyle: Physical Exercise Improves Mental Health
- The Effect of Topical Nicotine in Treatment of Early Parkinson's Disease
- Effect of CPAP on Reurrence of Afib in Patients with OSA

Pinpointing the Most Effective Treatment for Acne Vulgaris

Comparative Efficacy of Pharmacological Treatments for Acne Vulgaris: A Network Meta-Analysis of 221 Randomized Controlled Trials

Huang CY, Chang IJ, Bolick N, et al. Comparative Efficacy of Pharmacological Treatments for Acne Vulgaris: A Network Meta-Analysis of 221 Randomized Controlled Trials. *Ann Fam Med.* 2023;21(4):358-369. doi:10.1370/afm.2995

KEY TAKEAWAY: Oral isotretinoin is the most effective therapy for the treatment of acne vulgaris. Triple therapy consisting of topical antibiotics (abx), retinoids, and benzoyl peroxide (BPO) is the second most effective option.

STUDY DESIGN: Network meta-analysis of 221 trials (N=65,601)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Acne vulgaris is a global disease that is not limited to a single demographic. Cases can vary significantly in severity, location, and resistance to treatment. Previous randomized control trials have shown pharmacological management to be more effective than non-pharmacological options, however, inconsistencies regarding the most effective therapy suggest the need for further investigation.

PATIENTS: Patients with acne vulgaris

INTERVENTION: Single or combination acne remedies

CONTROL: Placebo

PRIMARY OUTCOME: Acne lesions

Secondary Outcome: Treatment success

METHODS (BRIEF DESCRIPTION):

- The literature search and independent review included 221 trials of acne treatment.
- A network meta-analysis was performed to create a random-effects model including 37 treatments.
- Patients 10–38 years old (mean 20 years old) were included in the study.
- The intervention consisted of single or combination therapies of oral antibiotics, topical antibiotics, topical retinoids, oral isotretinoin, hormonal agents, BPO, and azelaic acid.
- One reference treatment was used as the control.
- The primary outcome was the reduction of acne lesions which were categorized as total lesions, inflammatory lesions, and noninflammatory lesions.
- The secondary outcome of treatment success was defined as a two-grade improvement on the Investigator's Global Assessment (IGA) or reaching "clear" or "almost clear".
    - The IGA rates acne severity on a five-point scale which indicates severe, moderate, mild, almost clear, and clear.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 2–48 weeks (mean 12 weeks)

RESULTS:

Primary Outcome –

- The following treatments improved the total number of acne lesions compared to placebo:
    - Oral isotretinoin (mean difference [MD] 48; 95% CI, 36–60)
    - Topical abx/retinoid/BPO (MD 38; 95% CI, 27–49)
    - Oral abx/topical retinoid/BPO (MD 35; 95% CI, 22–48)
- The following treatments improved Inflammatory acne lesions compared to placebo:
    - Oral isotretinoin (MD 54; 95% CI, 43–66)
    - Topical abx/azelaic acid (MD 44; 95% CI, 32–55)
    - Oral abx/topical retinoid/BPO (MD 37; 95% CI, 26–48)
- The following treatments improved noninflammatory acne lesions compared to placebo:
    - Oral isotretinoin (MD 48; 95% CI, 37–60)
    - Topical abx/retinoid/BPO (MD 33; 95% CI, 25–41)
    - Oral abx/topical retinoid/BPO (MD 30; 95% CI, 18–42)
- Treatment success was highest with the following treatments:
    - Topical abx/retinoid/BPO (odds ratio [OR] 7; 95% CI, 4–11)
    - Oral abx/topical retinoid/BPO (OR 6; 95% CI, 3–12)
    - Topical nadifloxacin/BPO (OR 7; 95% CI, 2–19)

LIMITATIONS:

- Dosing was not taken into consideration.
- The average length of treatment was only 12 weeks, while acne vulgaris is a chronic condition.
- The placebo was not described.
- Side effects of these medications may limit adherence, ultimately skewing efficacy data.
- Gender, age, and geographical location were not compared to determine if treatment efficacy differs based on these factors.

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Wellness Is an Active Lifestyle: Physical Exercise Improves Mental Health

Effectiveness of Physical Activity Interventions for Improving Depression, Anxiety, and Distress: An Overview of Systematic Reviews

Singh B, Olds T, Curtis R, et al. Effectiveness of physical activity interventions for improving depression, anxiety and distress: an overview of systematic reviews. *Br J Sports Med.* 2023;57(18):1203-1209. doi:10.1136/bjsports-2022-106195

KEY TAKEAWAY: Physical activity appears to improve symptoms of depression and anxiety among adults with chronic diseases, mental health disorders, and healthy adults.

STUDY DESIGN: Umbrella review of meta-analyses of randomized controlled trials (RCTs) (N=128,119)

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

BRIEF BACKGROUND INFORMATION: Clinical practice guidelines for the treatment of depression and anxiety vary in the relative importance they assign to lifestyle treatments versus pharmacotherapy and psychotherapy. Wide adoption of physical activity as a treatment has lagged despite evidence for its benefits and advantages over conventional treatments. This umbrella review provides a comprehensive synthesis of the effects of different modes of physical activity on depression, anxiety, and psychological distress in adults.

PATIENTS: Adults

INTERVENTION: Various physical activity modalities

CONTROL: Usual care or non-physical activity

PRIMARY OUTCOME: Self-reported or clinician-rated symptoms of depression, anxiety, or psychological stress

METHODS (BRIEF DESCRIPTION)

- These authors conducted an umbrella review of meta-analyses of randomized controlled trials after searching 12 databases.
- 1,280 studies were identified, of which 97 meta-analyses met eligibility criteria. The eligible studies included 1,039 unique RCTs.
- Studies included were systematic reviews with meta-analyses of physical activity interventions for adults (≥18 years old), regardless of physical activity modality, supervision, delivery, and dose.
- Included participants were healthy individuals, those with chronic medical conditions, and/or behavioral health conditions.
- The authors excluded reviews with RCTs that combined physical activity with another intervention or that evaluated single bouts of exercise and reviews were excluded if >25% of component RCTs compared physical activity to pharmacotherapy interventions or compared two equal dose physical activities (e.g., aerobics vs resistance) without a non-physical activity control.
- Risk of bias was assessed using the A MeaSurement Tool to Assess Systematic Reviews (AMSTAR-2) tool, with ratings spanning 'critically low,' 'low,' 'moderate,' and 'high confidence.'
- Overlap of component RCTs was assessed using the Corrected Covered Area (CCA) method, with a score of 100% indicating every component review comprised the same component RCTs and a score of 0% indicating every component review comprised unique RCTs.
- The outcomes that were assessed measured the effect of exercise on depression, anxiety, and psychological distress using several clinical instruments to measure these outcomes.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 10 days to 24 months

RESULTS:

Primary Outcome –

- Compared to control, physical activity had a medium effect size for:
  - Reducing depressive symptoms (72 studies, N=62,040; standardized mean difference [SMD] –0.43; interquartile range [IQR] –0.66 to – 0.27)
  - Reducing anxiety (28 studies, N=10,952; SMD – 0.42; IQR –0.66 to –0.26)
- For psychological distress, one systematic review showed that physical activity had a medium effect size for reducing symptoms (1 study, N=508; SMD – 0.60; 95% CI, –0.78 to –0.42), whereas another systematic review showed no significant effect of physical activity (mean difference [MD] –0.30; 95% CI, –5.6 to 5.0) compared to usual care.

- The CCA was 0.6%, indicating a slight overlap of component RCTs across studies.
- Funnel plots did not have significant asymmetries or missing sections to indicate publication bias.

LIMITATIONS:

- Most component meta-analyses focused on mild-to-moderate depression, so subgroup analyses for anxiety and psychological distress were limited.
- Most component meta-analyses were 'critically low' on the AMSTAR-2 tool assessing risk of bias.
- There is questionable clinical significance given SMD of –0.43 points.

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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.

The Effect of Topical Nicotine in Treatment of Early Parkinson's Disease

Transdermal Nicotine Treatment and Progression of Early Parkinson's Disease

Oertel WH, Müller HH, Unger MM, et al. Transdermal Nicotine Treatment and Progression of Early Parkinson's Disease. *NEJM Evid*. 2023;2(9):EVIDoa2200311. doi:10.1056/EVIDoa2200311

KEY TAKEAWAY: Transdermal nicotine does not prevent early Parkinson's disease progression.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, multicenter trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There is no curative treatment for Parkinson's disease. Some epidemiological studies noticed the prevalence of Parkinson's was smaller in smokers compared to nonsmokers. There has been a positive effect seen in animal models, but there have been no human trials comparing nicotine to placebo in patients with early Parkinson's. This trial tested whether the transdermal nicotine will slow down the progression of early Parkinson's disease.

PATIENTS: Early-stage Parkinson's patients

INTERVENTION: Transdermal nicotine patches

CONTROL: Transdermal placebo patches

PRIMARY OUTCOME: Disease progression

Secondary Outcome: Motor and non-motor disease outcomes

METHODS (BRIEF DESCRIPTION):

- Patients diagnosed within the last 18 months, >30 years old without any medication treatment except monoamine oxidase B inhibitors (MAOBi) in Germany and the USA were included in the study.
- Patients were blinded and randomized to one of the following treatments:
  - Daily transdermal nicotine 7–28 mg/day for 60 weeks
  - Daily transdermal placebo seven or 28 mg/day for 60 weeks
- Disease progress was measured using the Unified Parkinson's Disease Rating Scale Parts I-III (UPDRS). Scores range from 0–172 with higher scores indicating greater impairment.
  - The UPDRS score was measured at baseline, at 52 weeks, and at 60 weeks.
- The frequency of adverse effects, Parkinson's disease questionnaire, and scales for outcomes of Parkinson's disease were measured through the clinical trial.
  - Parkinson's Disease Cognition (SCOPA-COG): Scores range from 0–43 with higher scores reflecting a better performance.
  - Beck Depression Inventory-II (BDI-II): Scores range from 0–63 with higher scores indicating a higher degree of depression.
  - Parkinson's Disease Questionnaire-8 (PDQ-8): Scores range from 0–32 with higher scores signifying poorer quality of life.
  - Parkinson's Disease Sleep Scale-2 (PDSS-2): Scores range from 0–60 with higher scores indicating higher sleep disturbance.

INTERVENTION (# IN THE GROUP): 79

COMPARISON (# IN THE GROUP): 83

FOLLOW-UP PERIOD: 60 weeks

RESULTS:

Primary Outcome –

- Transdermal nicotine patch treatment failed to slow early Parkinson's disease compared to the placebo group (mean difference [MD] –3; 95% CI, –6 to 0).

Secondary Outcome –

- There were no differences in motor and non-motor disease outcomes between nicotine and placebo.

LIMITATIONS:

- The effect of nicotine can only be tested by transdermal patches instead of smoking.
- No serum nicotine levels were drawn to control the effective dose.
- Participants' self-administering patches made the serum metabolites of nicotine more variable.
- Most patients dropped out of the trial due to discontinuation or adverse events.

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Effect of CPAP on Recurrence of Afib in Patients with OSA

Effect of Continuous Positive Airway Pressure Therapy on Recurrence of Atrial Fibrillation After Pulmonary Vein Isolation in Patients with Obstructive Sleep Apnea: A Randomized Controlled Trial

Hunt TE, Traaen GM, Aakerøy L, et al. Effect of continuous positive airway pressure therapy on recurrence of atrial fibrillation after pulmonary vein isolation in patients with obstructive sleep apnea: A randomized controlled trial. *Heart Rhythm.* 2022;19(9):1433-1441. doi:10.1016/j.hrthm.2022.06.016

KEY TAKEAWAY: Continuous positive airway pressure (CPAP) treatment reduces apnea-hypopnea index but doesn't lower atrial fibrillation (AF) recurrence or the time in AF after pulmonary vein isolation (PVI).

STUDY DESIGN: Randomized, controlled, open-label, parallel-group trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size, lack of generalizability, and lack of blinding)

BRIEF BACKGROUND INFORMATION: Atrial fibrillation has significant health risks, like heart failure and stroke. Catheter ablation with pulmonary vein isolation is a common treatment, but the relationship between AF and obstructive sleep apnea (OSA) complicates the treatment strategies available. Very little evidence is available on this topic and how to navigate patients dealing with this issue. This study examined how CPAP influences AF recurrence post-PVI in patients with OSA.

PATIENTS: Adults with AF and OSA

INTERVENTION: CPAP treatment

CONTROL: Standard care

PRIMARY OUTCOME: AF recurrence

Secondary Outcome: AF burden, CPAP quality of life

METHODS (BRIEF DESCRIPTION):

- The study involved 109 adults 18–75 years old with AF and OSA.
- Exclusion criteria included patients with unstoppable, coronary disease, transitory ischemic attack, stroke, structural heart disease, love ventricle systolic function, severe obesity (>40kg/m^2), and amiodarone use.
- Patients underwent a one-week CPAP tolerance test before being randomly assigned to “CPAP treatment” or “standard care groups”.
- Based on these parameters individuals proceeded to PVI.
- Patients received CPAP treatment using ResMed's “Air Sense 10 Auto set device” with a pressure range of 3–15 cm H2O. The goal was to have a minimum of four hours per night of compliance.
- The standard care group received routine care without CPAP treatment.
- Both groups underwent PVI using cryoballoon ablation or radiofrequency ablation.
- Antiarrhythmic drugs were administered post-PVI; ablation was seen as a failure if drugs continued beyond the blanking period.
- The primary outcome was measured via implantable loop recorders (ILRs).
    - Recurrence is defined as any episode longer than two minutes of AF within 3–12 months post-PVI.
    - A clinically relevant reduction in recurrence is defined at >50%.
- The secondary outcomes were measured as:
    - Total Burden of AF: Assessed by ILRs calculating time in AF. A high score indicates a greater burden of AF. This is expressed by a numerical value ranging from 3–30.
    - CPAP impact on quality of life: Evaluated using the following self-reported questionnaires
        - Atrial Fibrillation Severity Scale (AFSS): Measures severity of arrhythmia symptoms. Total AF burden score ranges from 3–30; higher scores indicate more severe symptoms.
        - 36-Item Short Form Health Survey (SF-36): Provides physical and mental component summary scores. Higher scores indicate a better quality of life.
        - Epworth Sleepiness Scale: Measures patients becoming sleepy throughout the day using an eight-situation questionnaire. A high score indicates a high likelihood of having sleep apnea. A low score indicates a low likelihood of having sleep apnea.
        - European Heart Rhythm Association (EHRA) scale: Classifies AF-related symptoms.

Relevant AF-related symptoms include palpitations or awareness of heartbeats, fatigue or tiredness, dyspnea or shortness of breath, chest discomfort or pain, dizziness or lightheadedness, syncope or fainting. A low EHRA score (Class I or II) indicates mild to no symptoms related to AF, these patients typically can engage in normal physical activity without significant limitation. A high EHRA score (Class III or IV) indicates moderate to severe symptoms patients in these classes experience limitations in their daily activities due to AF symptoms.

INTERVENTION (# IN THE GROUP): 55

COMPARISON (# IN THE GROUP): 54

FOLLOW-UP PERIOD:

- Five months before PVI (phase 1)
- 12 months after PVI (phase 2)

RESULTS:

Primary Outcome –

- There was no statistically significant difference in AF recurrence in the CPAP treatment group compared to standard care (odds ratio [OR] 1.0; 95% CI, 0.4–2.4).
- The probability of a clinically relevant AF recurrence with CPAP for OSAS after PVI was only 1.6%.

Secondary Outcome –

- There was no significant change in AF burden before PVI to follow up between the CPAP treatment group and the standard care group.
- There was no difference in quality of life between the CPAP treatment group and the standard care group.

LIMITATIONS:

- The study included mostly White, North European males, limiting the generalizability of results to the broader demographic.
- Using cryoballoon and radiofrequency ablation methods in different proportions may introduce variability
- A weekly CPAP tolerance test doesn't represent long-term adherence for most.
- The lack of blinding can introduce bias in patient-reported measures.

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