GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of January 2 - 6, 2023

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Pharmacotherapy for Treatment of Obesity: Show Me the Evidence

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Pharmacotherapy for Adults with Overweight and Obesity: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomized controlled trials. *Lancet* 2021; published online Dec 8. https://doi.org/10.1016/ S0140-6736(21)01640-8.

KEY TAKEAWAY: Phentermine-topiramate and GLP-1 receptor agonists produced the highest percentage of weight loss when coupled with lifestyle intervention in non-pregnant adults who are obese or overweight. Of the GLP-1 agonists, semaglutide may be the most effective. The risk of adverse drug events leading to discontinuation was highest among patients taking naltrexone-bupropion or phentermine-topiramate.

STUDY DESIGN: Systematic review and meta-analysis of 143 randomized controlled trials (N=49,810)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: In the existing landscape of weight loss medications, evidence for semaglutide and other agents has emerged. There has not been a recent comparison of the efficacy of existing and new agents for weight management.

PATIENTS: Overweight or obese non-pregnant adults

INTERVENTION: Weight loss medication + lifestyle modification

CONTROL: Lifestyle modification alone

PRIMARY OUTCOME: Change in body weight, adverse events leading to treatment discontinuation, weight regain, quality of life

Secondary Outcomes: Gastrointestinal (GI) events, severe GI events, body image, depression and anxiety symptoms

METHODS (BRIEF DESCRIPTION):

- Researchers utilized search criteria including terms related to weight loss and the medications of interest to search PubMed, Embase, ClinicalTrials.gov, and the Cochrane Library to find RCTs from inception to March 23, 2021.
- Included RCTs enrolled adults who were overweight or obese, regardless of weight-related complications.
- Weight loss agents were compared with lifestyle modifications or alternative weight loss agents for at least 12 weeks.
- Trials with a crossover design or that included participants with psychological conditions (schizophrenia, depression, eating disorders) were excluded.
- Investigators classified interventions utilizing the GRADE approach for rating certainty of evidence in four categories from high to very low.
    - The GRADE approach was also used to determine the magnitude of effect by assigning a minimal important difference (MID).

INTERVENTION (# IN THE GROUP): Unavailable

COMPARISON (# IN THE GROUP): Unavailable

FOLLOW UP PERIOD: Median 24 weeks (12–52 weeks)

RESULTS:

Primary Outcome – All agents lowered bodyweight compared to lifestyle modification alone, except for levocarnitine.

- Phentermine-topiramate was more effective to achieve at least 5% weight loss than lifestyle modifications (Odds Ratio [OR] 8.0; 95% CI, 5.2–12).
    - Phentermine-topiramate was more effective in achieving at least 10% weight loss than lifestyle modifications (OR 9.7; 95% CI, 6.0–16).
- GLP-1 receptor agonists were more effective for weight loss than lifestyle modifications (OR 6.3; 95%CI, 5.0–8.0).
    - GLP-1 receptor agonists were more effective for at least 10% weight loss than lifestyle modifications (OR 7.8; 95% CI, 5.9–10).
- Naltrexone-bupropion was more effective for at least 10% weight loss than lifestyle modifications (OR 5.2; 95% CI, 3.3–8.1).
- Phentermine-topiramate, naltrexone-bupropion, and GLP-1 receptor agonists had no statistically significant effect on quality of life compared to lifestyle modifications.
- Adverse effects were present in each of the treatment groups:
    - Phentermine-topiramate: 73 per 1,000 person-years
    - Naltrexone-bupropion: 61 per 1,000 person-years
    - GLP-1 receptor agonists: 52 per 1,000 person-years
    - Orlistat: 33 per 1,000 person-years
- There was no evidence for weight regain with orlistat or pramlintide.

Secondary Outcomes –

- Naltrexone-bupropion increased the risk for GI events compared to lifestyle modifications alone (OR 3.9; 95% CI, 2.9–5.1).
- Liraglutide increased the risk for GI events compared to lifestyle modifications alone (OR 3.1; 95% CI, 2.6–3.7).
- There were no differences in severe GI events or depression symptoms between any of the medications and lifestyle modifications alone.

LIMITATIONS:

- There was no evidence addressing body image or anxiety symptoms identified in the literature search.
- The RCTs had variable durations and were focused on disease-oriented outcomes.
- Few studies provided data on weight regain.
- There was a low certainty of evidence regarding improvements in HbA1c, LDL cholesterol, or blood pressure.

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Chronic Lower Back Pain: Exercises to Decrease Pain and Disability

Best Exercise Options for Reducing Pain and Disability in Adults with Chronic Low Back Pain: Pilates, Strength, Core-Based, and Mind-Body

Fernández-Rodríguez R, Álvarez-Bueno C, Cavero-Redondo I, et al. Best Exercise Options for Reducing Pain and Disability in Adults with Chronic Low Back Pain: Pilates, Strength, Core-Based, and Mind-Body. A Network Meta-analysis. *J Orthop Sports Phys Ther*. 2022;52(8):505-521. doi:10.2519/jospt.2022.10671

KEY TAKEAWAY: Pilates and mind-body effectively reduce pain in those with chronic lower back pain. Pilates and strength training reduce disability from back pain. It is recommended that these training sessions take place in sessions of less than 60 minutes, at least once or twice per week, for at least three to nine weeks.

STUDY DESIGN: Meta-analysis of 118 RCTs (N=9,710)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to lack of standardization and risk of bias in included trials)

BRIEF BACKGROUND INFORMATION: Exercise is currently recommended as one of the most effective short-term practices to reduce pain and disability in lower back pain. Lower back pain is the most common chronic pain and has the highest global burden of disease. The study aimed to determine the best type of exercise for reducing lower back pain to support clinical recommendations and decrease the burden of disease.

PATIENTS: Adults with chronic lower back pain

INTERVENTION: Structured physical exercise

CONTROL: No exercise or usual practice recommendations

PRIMARY OUTCOME: Pain and disability

METHODS (BRIEF DESCRIPTION):

- Adults from 35 countries 18–65 years old were included.
- The interventions consisted of the following:
  - Aerobic exercise (n=545)
  - Strength training (n=855)
  - Combined exercises (n=1,884)
  - Core-based exercises (n=1,374)
  - McKenzie exercises (n=222): Standardized approach for assessing and treating lower back pain through extension-based exercises.
  - Stretching (n=363)
  - Mind-body exercises (n=745): Focus on breathing, postural control, and movement accuracy
  - Pilates (n=758)
- The surface under the cumulative ranking curve (SUCRA) scores were used to assess each intervention and the interventions were ranked based on the scores.
  - The interventions were ranked, then assigned a numerical score between 0 and 1.
  - The best interventions would be valued close to 1 while the worst would be valued close to 0.

INTERVENTION (# IN THE GROUP): 6,750

COMPARISON (# IN THE GROUP): 2,960

FOLLOW UP PERIOD: Six to 150 weeks

RESULTS:

- Pilates was the most effective intervention for pain with a SUCRA score of 0.95 (SMD –0.83; 95% CI, –1.1 to –0.58).
- Mind-body exercises were the second most effective intervention for pain with a SUCRA score of 0.82 (SMD –0.97; 95% CI, –1.3 to –0.66).
- Pilates was the most effective intervention for disability with a SUCRA score of 0.99 (SMD –0.60; 95% CI, –0.82 to –0.38).
- Strength building exercises were the second most effective intervention for disability with a SUCRA score of 0.78 (SMD –0.61; 95% CI, –0.80 to –0.41).

LIMITATIONS:

- The lack of standardization between the studies required models and estimations to standardize findings, such as the SUCRA.
- The analysis states that two thirds of the trials were at a high risk of bias or concerns due to the lack of blinding and self-measured scales for pain and disability.

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Tralokinumab for Eczema

Tralokinumab Plus Topical Corticosteroids for the Treatment of Moderate-to-Severe Atopic Dermatitis: Results from the Double-Blind, Randomized, Multi-Centre, Placebo-Controlled Phase III ECZTRA 3 Trial

Silverberg JI, Toth D, Bieber T et al. ECZTRA 3 study investigators. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multi-centre, placebo-controlled phase III ECZTRA 3 trial. *Br J Dermatol* 2021 Mar;184(3):450-463.

KEY TAKEAWAY: Tralokinumab in combination with topical corticosteroids is effective and well tolerated in patients with moderate to severe atopic dermatitis compared to placebo.

STUDY DESIGN: Double blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current treatment guidelines for atopic dermatitis (AD) recommend topical corticosteroids (TCS) as first-line treatment combined with skin care. However, this is often insufficient to achieve control in patients with moderate-to-severe AD. Tralokinumab is a monoclonal antibody which has bene previously shown to be effective in a 12-week phase 2b trial.

PATIENTS: Adults with moderate to severe AD

INTERVENTION: Tralokinumab plus TCS

CONTROL: Placebo plus TCS

PRIMARY OUTCOME: Eczema improvement

Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Participants were recruited from 32 sites in Europe and North America.
  - The median age was 36 years old, and the population was 55% male and 76% White.
- Participants had moderate to severe AD for at least one year with inadequate response to TCS or systematic treatments.
- Participants were randomly assigned to subcutaneous tralokinumab 300 mg or placebo every two weeks.
- All participants were instructed to apply a thin layer of mometasone furoate 0.1% once daily as needed to areas of active AD lesions.
- Assessment of AD severity was performed by the study clinician every two weeks using the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI).
  - IGA: Scale of 0–5, with 0 being clear skin and 5 being severe AD
    - The primary outcome of improvement was defined as an IGA score of 0 or 1 at 16 weeks.
  - EASI: Scale of 0–72 measuring both the area involved and the severity of the ED lesion
    - The area score is a percentage for each area of head and neck, trunk, upper limbs, and lower limbs.
    - The severity score is the sum of the intensity scores for redness, thickness, scratching, and lichenification.
    - EASI-75 is defined as the proportion of patients achieving 75% improvement in their EASI score at 16 weeks.

INTERVENTION (# IN THE GROUP): 253

COMPARISON (# IN THE GROUP): 127

FOLLOW UP PERIOD: 16 weeks

RESULTS:

Primary Outcome –

- Tralokinumab resulted in more patients achieving eczema symptom improvement (per IGA) compared to placebo at 16 weeks (39% vs 26%, respectively; absolute difference 12%; 95% CI, 2.9–22).
- Tralokinumab resulted in more patients achieving at least 75% improvement of eczema symptoms (per EASI-75) compared to placebo (56% vs 36%, respectively; absolute difference 20%; 95% CI, 9.8–31).

Secondary Outcome –

- The overall frequency of adverse events was similar between tralokinumab and placebo treatments (71% vs 67%, respectively; no p-value provided).
- Serious adverse events were rare in both the tralokinumab and placebo groups (0.8% vs 3%, respectively; no p-value provided).

LIMITATIONS:

- There was no comparison made to dupilumab, the current FDA-approved biologic for AD.
- The study had a small sample size.
- The study was funded by LEO pharma which manufactures tralokinumab.

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Apixaban vs Rivaroxaban: A Comparison of Safety and Effectiveness in the Treatment of Acute VTE

Risk for Recurrent Venous Thromboembolism and Bleeding with Apixaban Compared with Rivaroxaban: An Analysis of Real-World Data

Dawwas GK, Leonard CE, Lewis JD, Cuker A. Risk for Recurrent Venous Thromboembolism and Bleeding with Apixaban Compared with Rivaroxaban: An Analysis of Real-World Data. *Ann Intern Med*. 2022;175(1):20-28. doi:10.7326/M21-0717

KEY TAKEAWAY: In the treatment of acute venous thromboembolism (VTE), apixaban is associated with fewer recurrent VTEs and bleeding events compared to rivaroxaban.

STUDY DESIGN: Retrospective new-user cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The direct oral anticoagulants (DOACs) apixaban and rivaroxaban are non-inferior compared to vitamin K antagonists like warfarin in the treatment of acute VTE. Previous comparisons of apixaban compared to rivaroxaban were limited in sample size, with 3,091 and 1,502 for apixaban and 12,164 and 6,682 for rivaroxaban. In contrast, this study used 36,236 subjects, with 18,618 each for apixaban and rivaroxaban.

PATIENTS: Adults diagnosed with VTE in the acute-care setting

INTERVENTION: Apixaban

CONTROL: Rivaroxaban

PRIMARY OUTCOME: Efficacy (composite of recurrent VTE either pulmonary embolism [PE] or deep vein thrombosis [DVT]) and safety (composite of either intracranial or gastrointestinal bleeding)

METHODS (BRIEF DESCRIPTION):

- Extracted data from claims database of a privately insured population in the United States.
- Inclusion: ICD-9 or ICD-10 code of primary diagnosis of VTE in an inpatient encounter plus prescription claim for either apixaban or rivaroxaban within 30 days of initial VTE diagnosis.
- Each sample given a propensity score to allow closest 1:1 pairing to reduce differences in baseline characteristics (caliper matching).
- Those with transient risk factors for provoked VTE were matched separately from those with chronic risk factors.
- Data collected from January 1, 2015 to June 30, 2020.
- Outpatient events were excluded.

INTERVENTION (# IN THE GROUP): 18,618 (out of 28,287 new users)

COMPARISON (# IN THE GROUP): 18,618 (out of 21,613 new users)

FOLLOW UP PERIOD: Median of 102 days for apixaban and 105 days for rivaroxaban

RESULTS:

- Efficacy: Apixaban resulted in fewer recurrent VTE events (composite of DVT and PE) than rivaroxaban (8.9 vs 11 person-years; HR 0.77; 95% CI, 0.69–0.87).
- Safety: Apixaban resulted in a lower rate of bleeding events (composite of intracranial and gastrointestinal bleeds) than rivaroxaban (7.2 vs 11 person-years; HR 0.60; 95% CI, 0.53–0.69).

LIMITATIONS:

- The cohort was restricted to commercially insured patients with VTE in the inpatient setting. Data was collected using inpatient discharge diagnosis codes.
- Outpatient claims for recurrent DVT and bleeds were not included.
- Adherence to apixaban and rivaroxaban was assessed by tracking prescription refill dates. There was no significant difference seen in refill frequency between the two groups.
- The original number of unmatched patients taking apixaban or rivaroxaban for VTE showed more people taking apixaban than rivaroxaban.
- Those taking apixaban were older and had more chronic disease than the rivaroxaban group. The effectiveness and safety profile of apixaban shown in this matched cohort may not generalize to the unmatched population.

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