GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

SABA, ICS, LABA, Oh My!

Combo Treatment or SABA Alone for Asthma?

To Cut or Not to Cut

Pulmonary Effects of Liraglutide in Obese COPD Patients

Is it Time to Replace BMI with Body Fat % as a Predictor of Mortality?

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SABA, ICS, LABA, Oh My! Combo Treatment or SABA Alone for Asthma?

Inhaled Reliever Therapies for Asthma: A Systematic Review and Meta-Analysis

Rayner DG, Ferri DM, Guyatt GH, et al. Inhaled Reliever Therapies for Asthma: A Systematic Review and Meta-Analysis. *JAMA*. 2025;333(2):143-152. doi:10.1001/jama.2024.22700

KEY TAKEAWAY: Combinations of inhaled corticosteroids (ICS) + formoterol and ICS + short-acting beta agonist (SABA) decrease the risk of asthma exacerbation compared to SABA alone, as well as improve asthma control.

STUDY DESIGN: Systematic review and meta-analysis of 27 randomized clinical trials (N=50,496)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Family physicians frequently treat asthma, a chronic condition which burdens millions of people, young and old. Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP) recommend ICS-formoterol over SABA as a reliever. The FDA also approved ICS-SABA recently as a reliever. However, data is lacking regarding which reliever is the best. This study aimed to evaluate asthma outcomes with ICS-SABA and ICS-formoterol compared to SABA alone.

PATIENTS: Children and adults with asthma

INTERVENTION: ICS + formoterol, ICS + SABA

CONTROL: SABA alone

PRIMARY OUTCOME: Risk for severe asthma exacerbation, asthma-related quality of life, asthma symptom control, adverse effects

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria were studies which tested inhaled asthma reliever therapies (SABA, ICS-SABA, Long-Acting Beta Agonist [LABA], ICS-LABA)
- Participants were 41 years old on average (mean 11–49 years old) and 41% were male.
- Exclusion criteria are not available.
- Duration and dosages for the intervention and comparator groups varied across studies.
- Frequency of usage was not specified.
- Risk for severe asthma exacerbation (emergency department visits, hospitalizations, systemic corticosteroid use) was stratified according to GINA 2024 guidelines. GINA step one was lower-risk and GINA step four was higher risk. Absolute risks of severe exacerbation were calculated for each step, with each therapy.
- Asthma symptom control was based on patient reports using the Asthma Control Questionnaire ACQ-5). Scores range from 0–6, with higher scores indicating worse control.
    - Minimum important difference: 0.5.
- Asthma-related quality of life was based on patient report using the Asthma Quality of Life Questionnaire AQLQ. Scores range from 1–7, with higher scores indicating better quality of life.
    - Minimum important difference: 0.5.
- Adverse effects included any vs serious vs discontinuation of inhaler 2/2 adverse event vs mortality. There is no description of how adverse effects were particularly analyzed in this study.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to determine certainty of evidence.

INTERVENTION (# IN THE GROUP):

- ICS + formoterol: 9,785
- ICS + SABA: 2,931

COMPARISON (# IN THE GROUP): 21,292

FOLLOW-UP PERIOD: 3–65 weeks

RESULTS:

Primary Outcome –

- ICS-SABA decreased the risk of severe asthma exacerbation compared to SABA alone (risk ratio [RR] 0.84; 95% CI, 0.73–0.95).
- ICS-formoterol decreased the risk of severe asthma exacerbation compared to SABA alone (RR 0.65; 95% CI, 0.60–0.72).
- ICS-formoterol decreased the risk of severe exacerbation when indirectly compared to ICS-SABA (RR 0.78; 95% CI, 0.66–0.92).
- ICS-SABA improved asthma control compared to SABA alone (RR 1.1; 95% CI, 1.03–1.2).
- ICS-formoterol improved asthma control compared to SABA alone (RR 1.1; 95% CI, 1.04–1.1).
- ICS-SABA did not significantly affect asthma-related quality of life compared to SABA alone (mean difference [MD] 0.07; 95% CI, –0.06 to 0.19).

- ICS-formoterol did not significantly affect asthma-related quality of life compared to SABA alone (MD 0.04; 95% CI, –0.04 to 0.13).
- ICS-SABA did not significantly affect overall and serious adverse effects compared to SABA alone
  - Overall adverse events (risk difference [RD] 0.5%; 95% CI, –4.4 to 5.4)
  - Serious adverse events (RD 0%; 95% CI, –1.1 to 1.2)
- ICS-formoterol did not significantly affect overall and serious adverse effects compared to SABA alone
  - Overall adverse events (RD –1.5; 95% CI, –3.5 to 1.0)
  - Serious adverse events (RD –0.6; 95% CI, –1.3 to 0).

LIMITATIONS:

- Only two studies solely evaluated pediatric patients.
- Formoterol was the only type of LABA used.
- Levalbuterol (a SABA) was not included/evaluated.
- This study did not compare ICS-formoterol and ICS-SABA directly.
- Concurrent albuterol-ipratropium administration in the studies is unknown.
- The need for oral corticosteroids for asthma exacerbation was based on physician discretion.
- Only outpatient settings were evaluated.
- There were dose differences and unspecified doses when comparing study to study.
- Presence, absence, history of, and quantity of smoking were not considered in most of these studies.
- Disease severity was not stratified when studying asthma symptom control, quality of life, and adverse effects.

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To Cut or Not to Cut

Surgery Versus Corticosteroid Injection for Carpal Tunnel Syndrome (DISTRICTS): An Open-Label, Multicenter, Randomized Controlled Trial

Palmbergen WAC, Beekman R, Heeren AM, et al. Surgery Versus Corticosteroid Injection for Carpal Tunnel Syndrome (DISTRICTS): An Open-label, Multicentre, Randomized Controlled Trial. *Lancet*. 2025;405(10495):2153-2163. doi:10.1016/S0140-6736(25)00368-X

KEY TAKEAWAY: Surgery improves recovery compared to corticosteroid injections in patients with carpal tunnel syndrome (CTS).

STUDY DESIGN: Multicenter, open-label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Surgery and corticosteroid injections are well-established, effective treatment options for CTS but whether one approach is significantly superior is unknown. This study aimed to compare the effectiveness these two treatments.

PATIENTS: Patients diagnosed with CTS

INTERVENTION: Surgery

CONTROL: Corticosteroid injections

PRIMARY OUTCOME: Recovery at 18 months

Secondary Outcome: Time to recovery, upper limb function, global perception of recovery, participant satisfaction, adverse events

METHODS (BRIEF DESCRIPTION):

- Adults diagnosed with CTS for at least six weeks and confirmed by electrophysiological or sonographic testing were included in the study.
- If carpal tunnel syndrome was bilateral, most severe or dominant hand was chosen for treatment.
- Patients were excluded if they had previous carpal tunnel surgery or corticosteroid injection on the ipsilateral wrist within the last year.
- Patients recruited from neurology outpatient clinics.
- Patients randomly assigned in a 1:1 ratio through the web-based application ALEA Clinical software then stratified according to unilateral or bilateral carpal tunnel syndrome.
- For those treated with surgery, any surgeon or technique in the common practice was allowed.
- For those treated with corticosteroid injections, any brand and dose was allowed, with or without local anesthetic.
- Either treatment could be followed by additional treatments as decided by the treating physician and patient.
- Additional treatment options could include injections, surgery, splints, physiotherapy, or any other treatment as determined by the patient or treating physician.
- Recovery at 18 months with recovery defined as a score <8 using a six-item Carpal Tunnel Symptoms scale (CTS-6). Scores range from 6–30, with higher scores indicating worse symptoms.
- Time to recovery determined by when first report of CTS-6 score of <8 was achieved
- Upper limb functioning determined using an 11-item measure of upper limb functioning. Scores range from 0–100, with higher scores indicating increased disability.
- Participants' perception of recovery and overall satisfaction were measured with seven-point Likert-type scale. Scores range from 1–7, with higher scores indicating higher satisfaction.
- Adverse events reported by physicians during procedures and by patients during follow up.

INTERVENTION (# IN THE GROUP): 468

COMPARISON (# IN THE GROUP): 466

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- Surgery improved recovery at 18 months compared to corticosteroid injection (relative risk [RR] 1.4; 95% CI, 1.2–1.6).

Secondary Outcome –

- Surgery resulted in a shorter median recovery time than corticosteroid injection:
  - Surgery (9.0 months; 95% CI, 7.7–10).
  - Corticosteroid injection (18 months; 95% CI, 16–20).
- Surgery improved upper limb function compared to corticosteroid injection (mean difference [MD] –7.4; 95% CI, –10 to –4.7).

- Surgery improved patient satisfaction compared to corticosteroid injection (MD 0.61; 95% CI, 0.37–0.84).
- There was no significant difference in global perception of recovery, and any physician reported adverse events between surgery and corticosteroid injection.
- For the participants who reported adverse effects only skin/wound problems showed any significant difference between the groups occurring significantly more commonly in the surgical group (RR 0.07; 95% CI, 0.03–0.11).

LIMITATIONS:

- Because of the nature of the treatment, participants and researchers were unable to be blinded to treatment.
- The endpoint assessment was not masked.
- Incomplete registration of eligible patients and reasons for non-participation.
- Race and ethnicity data were not collected.
- Choice of follow up duration was arbitrary.
- There was a lot of cross over therapy (injections in the surgery group and vice versa).

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Pulmonary Effects of Liraglutide in Obese COPD Patients

Respiratory Effects of Treatment with a Glucagon-Like Peptide-1 Receptor Agonist in Patients Suffering from Obesity and Chronic Obstructive Pulmonary Disease

Altintas Dogan AD, Hilberg O, Hess S, Jensen TT, Bladbjerg EM, Juhl CB. Respiratory Effects of Treatment with a Glucagon-Like Peptide-1 Receptor Agonist in Patients Suffering from Obesity and Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:405-414. Published 2022 Feb 22. doi:10.2147/COPD.S350133

KEY TAKEAWAY: Liraglutide may offer pulmonary benefits in obese chronic obstructive pulmonary disease (COPD) patients via improved lung mechanics. Liraglutide to treat COPD is not currently FDA approved.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, two-center trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to low sample size and limited power)

BRIEF BACKGROUND INFORMATION: COPD often coexists with obesity, contributing to reduced quality of life, limited physical activity, and frequent exacerbations. Liraglutide, a glucagon-like peptide- 1 (GLP-1) receptor agonist approved for weight loss and type-2 diabetes, also has potential anti-inflammatory effects. This study examined liraglutide's impact on lung function in patients with both obesity and COPD.

PATIENTS: Obese COPD patients

INTERVENTION: Liraglutide

CONTROL: Placebo

PRIMARY OUTCOME: Pulmonary function, physical capacity

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria included participants with COPD, body mass index (BMI) >27, 30–75 years old, ≥20 pack-year ex-smokers, and non-diabetics.
- Exclusion criteria included participants receiving long-term systemic corticosteroids, diabetes of any type, interstitial pulmonary disease, asthma, or asthma-COPD-overlap syndrome (ACOS). Additional exclusion criteria were severe hepatic, renal, or cardiac disease, a prior history of pancreatitis, and pregnancy or breastfeeding.
- 40 patients from two outpatient clinics were randomized 1:1 to receive subcutaneous liraglutide or placebo for 40 weeks.
- Liraglutide was titrated each week by 0.6 mg daily to reach a maximum of 3.0 mg daily by week four and maintained through week 40.
- Assessments were performed at baseline, weeks four, 20, 40 (end of trial), and week 44 (post-treatment).
- Pulmonary function and physical capacity were measured using the following:
  - Spirometry was measured as forced expiration volume in one second (FEV1), forced expiratory volume (FVC), FEV1/FVC ratio.
  - Diffusion was measured as capacity of lungs for carbon monoxide (DLCO).
  - COPD severity was measured using the COPD Assessment Test (CAT). Score range from 0–40, with higher scores corresponding to worsening COPD.
  - Six-minute walk test
  - Serum inflammatory markers were measured as C reactive protein (CRP), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1).
  - Body plethysmography was measured as total lung capacity (TLC), residual volume (RV).

INTERVENTION (# IN THE GROUP): 20

COMPARISON (# IN THE GROUP): 20

FOLLOW-UP PERIOD: 44 weeks

RESULTS:

Primary Outcome –

- Liraglutide improved some indices of pulmonary function and physical capacity compared to placebo.
  - Liraglutide increased FVC compared to placebo at 40 weeks (adjusted group difference 7.7%; p=.018).
  - Liraglutide preserved DLCO compared to placebo at 40 weeks (between-group difference 9.7%; p=.012).
  - Liraglutide improved COPD severity compared to placebo at 40 weeks (adjusted group difference 3.9 points; p=.012).
  - Liraglutide did not maintain its superiority over placebo in FVC, DLCO, or COPD severity at week

44, after being off treatment for 4 weeks (no statistical analysis completed).
    - Liraglutide did not improve the six-minute walk test compared to placebo at 40 weeks (between-group difference 47 meters; *p*=.075).
    - Liraglutide did not improve CRP, IL-6, or MCP-1 compared to placebo (no statistical analysis completed).
    - Liraglutide reduced RV compared to placebo at week 44 (adjusted group difference 20%; *p*=.039, which was not present at week 40.
    - Liraglutide reduced TLC compared to placebo at week 44 (adjusted group difference 9.1%; *p*=.013), which was not present at week 40.

LIMITATIONS:

- Small sample size and reduced statistical power.
- Between-group differences for pulmonary indices were reported without reporting the individual values for the liraglutide and placebo groups separately, confounding interpretation of p-values.
- Drop-out rate (25%) exceeded expected 20%.
- Short-term follow-up limits assessment of long-term effects.
- Exclusion of diabetic patients and active smokers limits generalizability of the study's findings.
- The proportion of groups that received treatment for acute COPD exacerbation remains unclear.
- Weight loss alone may not fully explain the observed improvement in treatment group.

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Is it Time to Replace BMI with Body Fat % as a Predictor of Mortality?

Body Mass Index vs Body Fat Percentage as a Predictor of Mortality in Adults Aged 20-49 Years

Mainous AG 3rd, Yin L, Wu V, et al. Body Mass Index vs Body Fat Percentage as a Predictor of Mortality in Adults Aged 20-49 Years. *Ann Fam Med*. 2025;23(4):337-343. Published 2025 Jul 28. doi:10.1370/afm.240330

KEY TAKEAWAY: Body fat percentage and waist circumference are stronger metrics for predicting all-cause and cardiovascular mortality in young adults than body mass index (BMI).

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: BMI can misclassify individuals with certain physiques as overweight or obese. Certain individuals with a normal BMI and elevated body fat percentage may be unaware of their significantly increased risk of metabolic syndrome such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). This study aimed to examine the use of body fat percentage vs BMI as a better predictor of mortality.

PATIENTS: Adult US population

INTERVENTION: Body fat percentage

CONTROL: BMI

PRIMARY OUTCOME: Mortality risk

METHODS (BRIEF DESCRIPTION):

- 4,252 adults 20–49 years old from the National Health and Nutrition Examination Survey (NHANES) 1999–2004, linked to the National Death Index through December 31, 2019, were included in the study.
- No treatments or interventions were received by either group.
- Body composition was measured using either body fat percentage or BMI.
- Healthy BMI was defined as between 19–25 kg/m^2, and overweight/obese was defined as ≥25 kg/m2.
- Healthy body fat percentage was defined as <27% in men and <44% in women, and unhealthy was defined as ≥27% in men and ≥44% in women. This was determined using Bioelectrical Impedance Analysis (BIA).
- Healthy waist circumference was defined as ≤40 inches in men and ≤35 inches in women, and unhealthy was defined as >40 inches in men and >35 inches in women.
- All-cause mortality, heart disease mortality, and cancer mortality were all examined at the 15-year mark to create consistency among the follow-up periods.
- Results were analyzed using hazard regression and adjusted based on age, race, and poverty status.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 15 years

RESULTS:

Primary Outcome –

- Higher body fat percentage and higher waist circumference increased the risk of all-cause mortality compared to higher BMI.
  - Body fat percentage (hazard ratio [HR] 1.8; 95% CI, 1.3–2.5)
  - Waist circumference (HR: 1.6; 95% CI, 1.1–2.3)
- Higher body fat percentage and higher waist circumference increased the risk of heart disease compared to higher BMI.
  - Body fat percentage (HR: 3.6; 95% CI, 1.5–8.5)
  - Waist circumference (HR 4.0; 95% CI, 1.9–8.3)
- Body fat percentage, waist circumference, and BMI did not significantly predict cancer mortality.
  - Body fat percentage (HR 1.3; 95% CI, 0.68–2.5)
  - Waist circumference (HR 0.68; 95% CI, 0.31–1.5)
  - BMI (HR 0.78; 95% CI, 0.40–1.5)

LIMITATIONS:

- Values used to determine healthy vs unhealthy body fat percentage were derived from a systematic review and meta-analysis that focused on mortality, so they are not formalized units like BMI and waist circumference.
- Study population was limited to only adults 20–49 years old.
- Mortality was the only outcome studied, and including morbidity may help determine body fat percentage as a predictor for the development of disease.

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