POEMs

Patient-Oriented Evidence That Matters

Long-Acting Muscarinic Antagonists Plus Inhaled Steroids Are Equivalent to Long-Acting Beta Agonists Plus Inhaled Steroids

Clinical Question

Are long-acting muscarinic antagonists a useful adjunct therapy to inhaled corticosteroids in patients 12 years or older with persistent asthma?

Bottom Line

Long-acting muscarinic antagonists added to inhaled corticosteroids are a superior treatment to placebo for improving asthma control in adults and children 12 years or older. Long-acting muscarinic antagonist add-on therapy is not superior to long-acting beta agonist (LABA) add-on therapy. The addition of long-acting muscarinic antagonists in patients already receiving LABA plus inhaled corticosteroids (triple therapy) does not further improve asthma control. (Level of Evidence = 1a)

Synopsis

Since 2014, a number of long-acting muscarinic antagonists (e.g., tiotropium [Spiriva], umeclidinium [Incruse], aclidinium [Tudorza]) have been marketed for the treatment of asthma. Investigators thoroughly searched multiple sources, including Medline, Embase, the Cochrane databases, clinical trial registries, manufacturers' data, and bibliographic references for studies that compared long-acting muscarinic antagonist therapy with placebo or other controllers as an add-on therapy to inhaled corticosteroids in patients at least 12 years of age with uncontrolled persistent asthma. No language restrictions were applied. Two reviewers independently evaluated potential studies for inclusion and used a standard scoring tool to assess methodologic quality. Disagreements were resolved by consensus discussion with a third reviewer. A total of 15 randomized controlled trials (N = 7,122 patients) met inclusion criteria. Of these, three received a high risk of bias score, with the remaining scoring at low risk of bias.

Adding a long-acting muscarinic antagonist to inhaled corticosteroids compared with adding placebo was significantly associated with a reduced risk of asthma exacerbation requiring systemic corticosteroids (relative risk = 0.67; 95% confidence interval, 0.48 to 0.92). There were no significant differences in rescue medication use or quality-of-life scores between add-on long-acting muscarinic antagonist therapy and add-on placebo. When comparing long-acting muscarinic antagonists to LABA as add-on therapy to inhaled corticosteroids, there was no significant difference in risk of asthma exacerbation requiring systemic corticosteroids, rescue medication use, or quality-of-life scores. Triple therapy with a long-acting muscarinic antagonist, LABA, and inhaled corticosteroids was not superior to LABA plus inhaled corticosteroids. Limiting the analysis to only studies with a low risk of bias did not change the results. A formal analysis for publication bias was not possible because of the small number of studies. Formal testing found minimal evidence of significant heterogeneity of results.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Government

Setting: Various (meta-analysis)

Reference: *Sobieraj DM, Baker WL, Nguyen E, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis [published correction appears in* JAMA. *2018;319(18):1939].* JAMA. *2018;319(14):1473-1484.*

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Cannabinoids Somewhat Helpful for Nausea, Maybe Helpful for Spasticity, Probably Not Helpful for Nonneuropathic Pain

Clinical Question

What are the benefits and harms of cannabinoids?

Bottom Line

This umbrella review found a modest benefit of cannabinoids for the treatment of neuropathic pain; a greater benefit for the treatment of spasticity and nausea and vomiting; and substantial harms. The studies were extremely heterogeneous in terms of the comparators, dose, duration, and outcome measures, so any conclusions should be taken with a grain of salt. (Level of Evidence = 1a–)

Synopsis

This is an umbrella review, which is a systematic review of systematic reviews. The authors did a broad search and identified 31 systematic reviews of the benefits and harms of cannabinoids, each with at least two randomized controlled trials. The topics addressed included pain, nausea and vomiting, spasticity, and adverse events. Individual outcomes were addressed in between two and 28 studies and in 44 to 2,737 patients. Challenges of this approach include a variety of populations, interventions, doses, and comparators, as well as the challenge of masking patients to treatment assignment. Most meta-analyses found a modest benefit, approximately 0.4 to 0.8 points, compared with placebo. Such a small benefit is unlikely to be clinically meaningful because we usually look for at least a 1-point improvement on a 10-point scale. Studies were moderately heterogeneous, with approximately one-half finding some benefit and one-half finding no benefit (intervention implementation = 43%). Benefit was generally greater in studies of neuropathic pain. Studies on the treatment of nausea and vomiting primarily included chemotherapy patients and those receiving palliative care (number needed to treat [NNT] = 3 to 7). There was significant heterogeneity. There was some evidence of benefit for treatment of spasticity as measured by the outcome of responder vs. nonresponder (NNT = 7 to 10), although the reductions in a 10-point spasticity score were modest (0.31 to 0.76). Adverse events such as feeling high, disorientation, and confusion were relatively common (number needed to treat to harm [NNTH] = 2 to 15), although psychosis was relatively rare. The NNTH to discontinue the medication was between 8 and 22.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Unknown/not stated

Setting: Various (meta-analysis)

Reference: *Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: pain, nausea and vomiting, spasticity, and harms.* Can Fam Physician. *2018;64(2):e78-e94.*

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Five-Day Nitrofurantoin Superior to Single-Dose Fosfomycin for Women with Uncomplicated UTI

Clinical Question

Is a five-day course of nitrofurantoin as effective as single-dose fosfomycin (Monurol) in the treatment of women with uncomplicated lower urinary tract infection (UTI)?

Bottom Line

A five-day course of nitrofurantoin is significantly more likely than single-dose fosfomycin to achieve both clinical and microbiologic resolution of uncomplicated lower UTI in otherwise healthy adult women. (Level of Evidence = 1b–)

Synopsis

The investigators identified women, 18 years and older, who presented with at least one symptom of acute lower UTI, including dysuria, urgency, frequency, or suprapubic tenderness, and a urine dipstick result positive for nitrites or leukocyte esterase. Exclusion criteria included pregnancy, lactation, suspected upper UTI, antibiotic treatment for a UTI in the previous four weeks, indwelling urinary catheter, or immunosuppression. The patients randomly received (concealed allocation assignment) oral nitrofurantoin, 100 mg three times daily for five days, or a single 3-g dose of oral fosfomycin. Although patients were directly aware of treatment group assignment (open-label), individuals masked to treatment group assignment assessed all outcomes, including the primary outcome of clinical resolution of all symptoms and signs of UTI without

prior failure. Complete follow-up occurred for 92% of patients at 28 days.

Using intention-to-treat and per-protocol analyses, significantly more patients in the nitrofurantoin group achieved clinical resolution than in the fosfomycin group (70% vs. 58%; number needed to treat = 8.1; 95% confidence interval, 4.8 to 25.9). Similarly, microbiologic resolution based on a negative urine culture occurred significantly more often in patients treated with nitrofurantoin. No significant group differences occurred in the development of pyelonephritis or urosepsis. Adverse events were mild and occurred similarly in both treatment groups.

Study design: Randomized controlled trial (single-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (primary care)

Reference: *Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial.* JAMA. *2018;319(17):1781-1789.*

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Ambulatory Blood Pressure Important for Decision-Making About Treatment

Clinical Question

What is a better predictor of mortality: ambulatory or office-based measurement of blood pressure?

Bottom Line

This study supports the guidelines recommending that treatment decisions be based on ambulatory blood pressure measurements rather than in-office blood pressure results. The difference between the two measurements in this cohort was 19/11 mm Hg, which is enough to change the decision to prescribe a medication at all, or to add a second or third medication. (Level of Evidence = 2b)

Synopsis

How we measure things matters. For example, nonfasting lipid levels are a better predictor of mortality than fasting lipid levels. Recent guidelines for hypertension, including those from the U.S. Preventive Services Task Force, have emphasized the need to confirm elevated blood pressure in most patients using some form of ambulatory blood pressure monitoring. This study used data from a large Spanish hypertension registry to look at the association between clinic blood pressure, ambulatory blood pressure, and mortality. The registry includes adults with an indication for ambulatory blood pressure monitoring, such as suspected white coat hypertension, borderline or labile hypertension, or hypertension refractory to treatment. The registry supplies data on clinic blood pressure, measured by automated devices after five minutes of seated rest, and 24-hour ambulatory blood pressure measurements. These data were linked to national vital statistics databases to determine cardiovascular and all-cause mortality. The analysis was adjusted for comorbidities, age, sex, tobacco use, and body mass index. The mean age of patients was 58 years, 58% were male, and only 11% had a diagnosis of cardiovascular disease. During a median 4.7 years of follow-up, there were a total of 3,808 deaths, including 1,295 cardiovascular deaths. The mean ambulatory blood pressure was 129/76 mm Hg, compared with 148/87 mm Hg in the clinic. The clinic blood pressure was measured by an automated device after five minutes of rest, yet far higher than the ambulatory measurements. In the fully adjusted model that adjusted for clinic blood pressure, the hazard ratio for all-cause mortality was 1.58 (95% confidence interval [CI], 1.56 to 1.60) for the ambulatory systolic blood pressure vs. 1.02 (95% CI, 1.00 to 1.04) for the clinic systolic blood pressure adjusted for ambulatory blood pressure. A similar pattern was seen for diastolic blood pressure. The inflection point for an increase in both cardiovascular and all-cause mortality is at a systolic blood pressure of 140 mm Hg to 160 mm Hg. Mortality was not increased in patients with controlled hypertension but was increased in those with white-coat and masked (i.e., normal in clinic, abnormal at home) hypertension.

Study design: Cohort (prospective)

Funding source: Government

Setting: Population-based

Reference: *Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality.* N Engl J Med. *2018;378(16):1509-1520.*

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