POEMs

Patient-Oriented Evidence That Matters

Twenty-Year Follow-Up of the Women's Health Initiative Trials: Lower Breast Cancer Mortality with Estrogen Alone, No Difference with Estrogen Plus Progesterone

Clinical Question

Does hormone therapy increase the risk of breast cancer incidence and mortality in postmenopausal women?

Bottom Line

The cumulative 20-year follow-up report from the Women's Health Initiative hormone therapy trials found significantly lower breast cancer incidence and mortality among postmenopausal women who previously took conjugated equine estrogen (CEE; Premarin) alone (with a prior hysterectomy) than in women who took a placebo. Women in the same age group who took estrogen plus progesterone have a significantly increased incidence of breast cancer compared with those who took a placebo, but no significant difference in breast cancer mortality. (Level of Evidence = 1b)

Synopsis

The report is a 20-year median cumulative follow-up of the Women's Health Initiative hormone therapy trials that evaluated the outcomes from giving CEE plus progesterone to postmenopausal women, 50 to 79 years of age, with an intact uterus, and giving CEE alone to women in the same age group with a previous hysterectomy. The original trials were stopped after 7.2 years because of an increased risk of stroke in the treatment groups. After the original trials were stopped, less than 4% of the women reported continuing hormone therapy. The previous cumulative 18-year follow-up report showed no significant differences in all-cause mortality, cardiovascular-related mortality, or cancer-related mortality in postmenopausal women who took CEE plus progesterone or CEE alone (with a prior hysterectomy) compared with women who took a placebo. This additional follow-up report focuses on breast cancer incidence and mortality. Using data obtained from regular surveillance of the National Death Index and cancer registries, as well as reports from next of kin, information was available for more than 98% of the 27,347 original participants. Compared with placebo, CEE alone was associated with a statistically significant lower breast cancer incidence (hazard ratio [HR] = 0.78; 95% CI, 0.65 to 0.93) and breast cancer mortality (HR = 0.60; 95% CI, 0.37 to 0.97). CEE plus progesterone was associated with a statistically significant higher breast cancer incidence (HR = 1.28; 95% CI, 1.13 to 1.45), but no significant difference in breast cancer mortality.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials.* JAMA. *2020; 324(4):369-380.*

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Triple Inhaled Therapy Provides a Small Reduction in Moderate COPD Exacerbations, No Effect on Severe Exacerbations

Clinical Question

Is triple inhaled therapy for chronic obstructive pulmonary disease (COPD) more effective than dual inhaled therapy?

Bottom Line

Triple inhaled therapy, with budesonide (Pulmicort) in a dose of either 160 mcg or 320 mcg daily plus a long-acting muscarinic antagonist (LAMA) and a long-acting beta$_2$ agonist (LABA), reduces moderate exacerbations (a need for an antibiotic or steroid for three or more days) more than either a LAMA plus a LABA or inhaled corticosteroid plus a LABA, but the difference is small and of questionable clinical significance. There is no clinically important difference in severe exacerbations and no difference in mortality. Another study found a mortality reduction for

triple therapy, with numbers needed to treat for one year of 120 (vs. a LAMA plus a LABA) and 358 (vs. an inhaled corticosteroid plus a LABA). (Level of Evidence = 1b)

Synopsis

Triple inhaled therapy for COPD consists of an inhaled corticosteroid, a LAMA, and a LABA. The inhaled corticosteroid in this study was budesonide, the LAMA was glycopyrrolate, 9 mcg twice daily, and the LABA was formoterol (Breztri Aerosphere), 4.8 mcg twice daily. The study randomized 8,588 patients to one of four regimens: triple therapy with 320 mcg of budesonide daily, triple therapy with budesonide, 160 mcg daily, dual therapy with a LAMA plus a LABA, and dual therapy with an inhaled corticosteroid plus a LABA. Participants had COPD that was not well-controlled (forced expiratory volume in one second [FEV_1] less than 0.70 post-bronchodilator, and already taking at least two inhaled agents) and had experienced at least one moderate or severe exacerbation in the past year. Participants had a mean age of 64 years, approximately 60% were men, and 41% were current smokers. Approximately 30% of participants had a post-bronchodilator FEV_1 of 50% to 80% of predicted, 60% were at 30% to 50% of predicted, and 10% were less than 30% of predicted.

The primary outcome was the rate of moderate or severe exacerbations; severe involved hospitalization, whereas moderate was any exacerbation treated with three or more days of an antibiotic or systemic corticosteroid. Groups were balanced at baseline, but allocation concealment was not described. It is unclear why rates of exacerbation were analyzed by means of negative binomial regression instead of a straightforward comparison of the rates of the primary outcome between groups. After one year, there was no clinically significant difference between groups in the rate of severe exacerbations (0.13 to 0.16 per year in the four groups). There was a difference in the likelihood of moderate to severe exacerbations: 1.25 and 1.23 per year in the 320-mcg and 160-mcg triple therapy groups, respectively, compared with 1.63 in the LAMA plus LABA group, and 1.47 in the inhaled corticosteroid plus LABA group. In comparison with the inhaled corticosteroid plus LABA combination, that is approximately one fewer moderate or severe exacerbation every four years, but because there was no reduction in severe exacerbations, this is due to fewer moderate exacerbations. For the comparison with a LAMA plus a LABA, it is approximately one fewer moderate exacerbation every 2.5 years. Although this study was not powered to compare the budesonide dosages, the results were generally similar for the 160-mcg and the 320-mcg daily doses. There were no significant differences in mortality or serious adverse events.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Rabe KF, Martinez FJ, Ferguson GT, et al.; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD.* N Engl J Med. *2020;383(1):35-48.*

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Short-Term Low Back Pain Relief with Placebo

Clinical Question

Is placebo effective in patients with low back pain?

Bottom Line

Over three weeks, patients with long-term low back pain who knowingly took placebo twice a day reported less pain and disability than those continuing with treatment as usual. This is not the only study to show the benefit of placebo. Whether the benefit persists is not known. A nonprescription placebo (Zeebo) is available, or pharmacists can prepare placebo capsules. (Level of Evidence = 2b)

Synopsis

The authors enrolled 127 patients with long-term low back pain. More than 70% of enrollees reported having back pain for more than five years. The average age was 59 years and 60% were women. Initial pain scores were approximately 5 out of a possible 10, and roughly 20% of the patients were treated with analgesics at the time of enrollment. The patients were told before enrollment that the study would involve placebo treatment and were shown a video on the beneficial effects of placebo. They were then randomized, with allocation assignment unconcealed, to

receive existing care or existing care plus placebo to be taken twice daily for 21 days. The patients were told it was placebo. At the end of the study, a composite pain intensity score—comprising minimum, maximum, and average pain intensities during the past seven days on an 11-point scale—dropped more with placebo treatment than with existing care alone (0.62 vs. 0.11; $P = .001$), and subjective disability scores improved to a greater extent with placebo (3.21 decrease vs. 0.65 increase; $P = .02$). Objective mobility or anxiety and stress scores were not affected. The researchers did not mask the enrolling investigator to the treatment assignment at the time of enrollment (unconcealed allocation); randomization produced an imbalance in body mass index between the groups, which might have been due to chance or to selective enrollment of patients.

Study design: Randomized controlled trial (nonblinded)

Funding source: Government

Allocation: Unconcealed

Setting: Outpatient (specialty)

Reference: *Kleine-Borgmann J, Schmidt K, Hellmann A, et al. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial.* Pain. *2019;160(12):2891-2897.*

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Buffering Lidocaine 1%/Epinephrine with Sodium Bicarbonate in a 3:1 Ratio Is as Effective and Less Painful than a 9:1 Ratio

Clinical Question

Does a lower ratio of buffered lidocaine 1%/epinephrine 1:100,000 solution (Lido/Epi) to sodium bicarbonate ($NaHCO_3$) solution cause less pain during infiltration?

Bottom Line

Lido/Epi buffered with $NaHCO_3$ in a 3:1 ratio is significantly less painful during infiltration than unbuffered Lido/Epi and buffered Lido/Epi in a 9:1 ratio. The difference in mixing ratio does not change the length or quality of the anesthetic effect. There are no commercial products of Lido/Epi solutions with $NaHCO_3$ because the stability of the mixture is limited. All injection solutions in this study were given at room temperature. (Level of Evidence = 1b)

Synopsis

Lido/Epi is one of the most commonly used local anesthetics for office-based procedures. The acidic nature of lidocaine is thought to be responsible for the burning sensation during infiltration. $NaHCO_3$ is used as a buffering agent to minimize acidity and reduce pain during infiltration. The investigators recruited 48 healthy volunteers, 18 to 75 years of age, who randomly received (allocation concealed) either two or four infiltrations of 2-mL Lido/Epi buffered with $NaHCO_3$ at room temperature in mixing ratios of 3:1, 9:1, or 10:0 (unbuffered), or a placebo (sodium chloride 0.9%). Mixing occurred within one minute before infiltration, and the injections randomly occurred on various sites of the right and left forearm. All participants completed the trial and no serious adverse events occurred. Study participants rated the 3:1 mixture as significantly less painful than the 9:1 mixture (median pain score is 1.5 points lower on a 10-point scale, where 0 = no pain and 10 = unacceptable pain, when 3:1 mixture is given first, and 0.5 points lower when given second). The unbuffered mixture was more painful than the 3:1 and 9:1 mixtures, and the placebo mixture was notably the most painful of all the injections.

Study design: Crossover trial (randomized)

Funding source: Foundation

Allocation: Concealed

Setting: Outpatient (specialty)

Reference: *Vent A, Surber C, Graf Johansen NT, et al. Buffered lidocaine 1%/epinephrine 1:100,000 with sodium bicarbonate (sodium hydrogen carbonate) in a 3:1 ratio is less painful than a 9:1 ratio: a double-blind, randomized, placebo-controlled crossover trial.* J Am Acad Dermatol. *2020;83(1):159-165.*

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