POEMs

Patient-Oriented Evidence That Matters

Nirmatrelvir/Ritonavir Reduces Hospitalization, Mortality in Patients 65 Years and Older With COVID-19; Effect on Younger Patients Unclear

Clinical Question

Does nirmatrelvir/ritonavir (Paxlovid) improve outcomes in a largely vaccinated population of patients with COVID-19?

Bottom Line

Paxlovid reduces hospitalization and mortality in older, high-risk patients with COVID-19, but data in younger vaccinated patients are inconsistent. More studies are needed, particularly in patients 50 to 64 years of age. (Level of Evidence = 2b)

Synopsis

The primary study used to approve Paxlovid for use in outpatients with COVID-19 included only high-risk unvaccinated patients. The most recent study from a large health system in Israel identified adults 40 years and older who were eligible to receive the drug during the Omicron surge. It compared patients who received Paxlovid within five days of a confirmed diagnosis of COVID-19 with patients who did not. Overall, 78% of included patients had previous immunity by vaccination, prior infection, or both. The analysis was adjusted for comorbidities, demographics, ethnicity, religious affiliation, and socioeconomic status. Approximately 80% of participants were considered fully vaccinated. Data were stratified by age, and benefit was only seen in people 65 years and older. The rate of hospitalization (14.7 vs. 58.9 cases per 100,000 person-days; adjusted hazard ratio [HR] = 0.27; 95% CI, 0.15 to 0.49) and the risk of death (HR = 0.21; 95% CI, 0.05 to 0.82) were lower in this group. There was no difference in either outcome in patients 40 to 64 years of age. Past research has shown a higher overall risk for patients older than 50 years, but results for patients 50 to 64 years of age were not reported in this study. A second study from Hong Kong compared outcomes in outpatients given Paxlovid with those who were not treated. This study found lower rates of mortality (HR = 0.25; 95% CI, 0.13 to 0.47) and hospitalization (HR = 0.69; 95% CI, 0.60 to 0.79) in patients given Paxlovid. The study found no difference in benefit by age, although only approximately 20% of the patients in the study were younger than 65 years, and only 35% were fully vaccinated.

Study design: Cohort (retrospective)

Funding source: Self-funded or unfunded

Setting: Population-based

Reference: *Arbel R, Sagy YW, Hoshen M, et al. Nirmatrelvir use and severe covid-19 outcomes during the Omicron surge.* N Engl J Med. *2022;387(9):790-798.*

Mark H. Ebell, MD, MS
Professor
University of Georgia
Athens, Ga.

Amitriptyline, Duloxetine, and Pregabalin Each Effective in Decreasing Pain From Diabetic Peripheral Neuropathy; Combinations Even Better

Clinical Question

Are amitriptyline, duloxetine (Cymbalta), and pregabalin (Lyrica) effective in decreasing pain in adults with diabetic peripheral neuropathy?

Bottom Line

Adults with painful diabetic peripheral neuropathy had similar degrees of improvement with monotherapy using amitriptyline, duloxetine, and pregabalin. There was even greater improvement with subsequent combination therapy regardless of initial choice of medication. (Level of Evidence = 1b)

Synopsis

The researchers enrolled 130 adults with diabetes mellitus and pain associated with distal symmetric polyneuropathy for at least three months. In this crossover trial, the participants were randomly assigned to three 16-week pathways separated by a two-week washout period: oral amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin. Each pathway started with a two-week period in

which doses were titrated to the maximum tolerated dose. This was followed by six weeks of maintenance monotherapy. At the end of six weeks, those with a pain level of 3 or less out of 10 were classified as responders and remained on monotherapy for 10 weeks. Nonresponders received the second drug for 10 weeks. During the subsequent 10 weeks, the researchers titrated medication doses to maintain pain levels at 3 or less out of 10. At the end of 16 weeks, the researchers stopped all study drugs for a two-week washout period, and the participants started the next drug combination.

Most (84%) of the participants had type 2 diabetes and were White (94%). Although 130 started the first pathway, only 97 and 84 began a second and third pathway, respectively. At the end of six weeks of monotherapy, the proportion of responders was similar for amitriptyline (37%), duloxetine (32%), and pregabalin (34%). At the end of 16 weeks, the proportion of responders was similar for oral amitriptyline supplemented with pregabalin (48%), pregabalin supplemented with amitriptyline (47%), and duloxetine supplemented with pregabalin (43%). The authors found that at the end of each evaluation period, the participants had similar degrees of improvement in pain regardless of agent. Most adverse events were mild and similar across all three pathways, with the three exceptions summarized in the accompanying table.

Study design: Crossover trial (randomized)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Tesfaye S, Sloan G, Petrie J, et al.; OPTION-DM Trial Group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial [published correction appears in* Lancet. *2022;400(10355):810].* Lancet. *2022; 400(10353):680-690.*

Henry C. Barry, MD, MS
Professor
Michigan State University
East Lansing, Mich.

SUMMARY TABLE

Notable Adverse Events With Treatment for Diabetic Peripheral Neuropathy

Adverse event	Oral amitriptyline supplemented with pregabalin	Pregabalin supplemented with amitriptyline	Duloxetine supplemented with pregabalin	*P* value
Dizziness	12%	16%	24%	.036
Nausea	5%	23%	7%	.0011
Dry mouth	32%	8%	17%	.0003

Tocilizumab Beneficial for Adults With Persistent Polymyalgia Rheumatica Symptoms Who Receive Steroid Therapy

Clinical Question

Is tocilizumab (Actemra) effective for improving symptoms or reducing prednisone requirements in adults with active polymyalgia rheumatica (PMR) despite ongoing glucocorticoid therapy?

Bottom Line

The study found that intravenous tocilizumab every four weeks for 24 weeks significantly reduced symptoms of active PMR in adults despite ongoing prednisone therapy, resulting in a greater percentage of patients with reduced prednisone requirements. (Level of Evidence = 1b)

Synopsis

Effective alternative treatments for persistent PMR that requires long-term glucocorticoids are needed. The investigators identified adults older than 50 years who met the standard diagnostic criteria for PMR and had a C-reactive protein (CRP) level of at least 10 mg per L or an erythrocyte sedimentation rate of at least 20 mm per hour at disease onset. Eligible patients (N = 101) included those who responded to 12 to 25 mg per day of prednisone to attain a CRP level of less than 10 mg per L or an erythrocyte sedimentation rate of less than 20 mm per hour but subsequently developed glucocorticoid dependency with worsening disease activity after tapering to a prednisone dosage of less than 10 mg per day. Patients randomly received (concealed allocation assignment) an intravenous infusion of tocilizumab (8 mg per kg) every four weeks for 24 weeks or matched placebo. The primary outcome was a composite of disease activity, defined as a PMR activity score computed using the CRP level of less than 10 (range = 0 to 100; higher scores indicate greater disease activity; based on minutes of morning stiffness, ability to elevate upper limbs, physician global assessment, patient-reported pain, and CRP level), and a prednisone dosage of 5 mg per day or less or a prednisone dosage decrease of at least 10 mg vs. baseline. At weeks 12, 16, and 20, prednisone dosages greater than 10 mg per day were tapered by 5 mg. For patients who were already taking prednisone dosages of 10 mg per day or less and whose disease activity scores were less than 10, the prednisone dosage was decreased by 2 mg every two weeks. Individuals masked to treatment group assignment assessed outcomes. Complete follow-up occurred for all patients at 24 weeks.

Using intention-to-treat analysis, at 24 weeks the primary end point occurred significantly more often in patients treated with tocilizumab than in patients treated with placebo (67.3% vs. 31.4%, respectively; number needed to treat = 2.8; 95% CI, 1.9 to 6.1). No significant group differences occurred in adverse events leading to treatment discontinuation.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry and government

Allocation: Concealed

Setting: Outpatient (specialty)

Reference: *Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, et al. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: a randomized clinical trial.* JAMA. *2022;328(11):1053-1062.*

David C. Slawson, MD
Professor of Family Medicine
Atrium Health
Charlotte, N.C.

Polypill Better for Secondary Cardiovascular Prevention Than Physician-Directed Care

Clinical Question

Does giving a polypill containing aspirin, an angiotensin-converting enzyme inhibitor, and a high-intensity statin improve outcomes more than physician-directed care as secondary prevention in patients who have had a recent acute myocardial infarction (MI)?

Bottom Line

A polypill containing aspirin, an angiotensin-converting enzyme inhibitor, and a high-intensity statin resulted in fewer cardiovascular events in patients who had an acute MI in the past six months. (Level of Evidence = 1b)

Synopsis

The multicountry European study identified 2,499 participants with a history of MI in the past six months, who were older than 75 years or older than 65 years with at least one risk factor (e.g., diabetes mellitus; mild to moderate kidney failure; past MI, stroke, or revascularization). They were randomized into one of two groups. The first group received a polypill containing aspirin (100 mg), ramipril (Altace; 2.5 mg, 5 mg, or 10 mg), and atorvastatin (40 mg). The atorvastatin dose could be reduced to 20 mg at the discretion of the investigators, and the target dose for ramipril was 10 mg. The second group received usual care based on European guidelines. The average age of participants was 75 years, 69% were men, and more than 98% were White. Groups were balanced at baseline, outcomes were assessed by a committee masked to treatment group, and the analysis was by intention to treat. Participants were followed up for a median of three years. In the polypill group, 92% of patients received the 40-mg dose of atorvastatin; in the usual care group, 83% of patients received what was defined as a high-intensity statin. The use of aspirin was similar between groups. Most patients in the polypill group received ramipril at a 2.5-mg or 5-mg dose. The primary outcome of cardiovascular death, nonfatal stroke, nonfatal MI, or urgent revascularization occurred less often in the polypill group (9.5% vs. 12.7%; $P < .001$; number needed to treat = 31). All the components of the composite decreased similarly, including cardiovascular death (3.9% vs. 5.8%; hazard ratio = 0.67; 95% CI, 0.47 to 0.97; number needed to treat = 53). There was a trend toward more noncardiovascular deaths (5.4% vs. 3.7%; hazard ratio = 1.42; 95% CI, 0.97 to 2.07) and no difference in all-cause mortality.

Study design: Randomized controlled trial (single-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Castellano JM, Pocock SJ, Bhatt DL, et al.; SECURE Investigators. Polypill strategy in secondary cardiovascular prevention.* N Engl J Med. *2022;387(11):967-977.*

Mark H. Ebell, MD, MS
Professor
University of Georgia
Athens, Ga. ■