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Top 20 Research Studies of 2021 for Primary Care Physicians

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This article summarizes the top 20 research studies of 2021 identified as POEMs (patient-oriented evidence that matters) that did not address the COVID-19 pandemic. Sodium-glucose cotransporter 2 inhibitors and glucose-like peptide 1 receptor agonists prevent adverse cardiovascular and renal outcomes in patients with type 2 diabetes mellitus and also reduce all-cause and cardiovascular mortality. Most older adults (mean age, 75 years) with prediabetes do not progress to diabetes. Among patients in this age group with type 2 diabetes treated with medication, an A1C level of less than 7% is associated with increased risk of hospitalization for hypoglycemia, especially when using a sulfonylurea or insulin. For patients with chronic low back pain, exercise, nonsteroidal anti-inflammatory drugs, duloxetine, and opioids were shown to be more effective than control in achieving a 30% reduction in pain, but self-discontinuation of duloxetine and opioids was common. There is no clinically important difference between muscle relaxants and placebo in the treatment of nonspecific low back pain. In patients with chronic pain, low- to moderate-quality evidence supports exercise, yoga, massage, and mindfulness-based stress reduction. For acute musculoskeletal pain, acetaminophen, 1,000 mg, plus ibuprofen, 400 mg, without an opioid is a good option. Regarding screening for colorectal cancer, trial evidence supports performing fecal immunochemical testing every other year. For chronic constipation, evidence supports polyethylene glycol, senna, fiber supplements, magnesium-based products, and fruit-based products. The following abdominal symptoms carry a greater than 3% risk of cancer or inflammatory bowel disease: dysphagia or change in bowel habits in men; rectal bleeding in women; and abdominal pain, change in bowel habits, or dyspepsia in men and women older than 60 years. For secondary prevention in those with established arteriosclerotic cardiovascular disease, 81 mg of aspirin daily appears to be effective. The Framingham Risk Score and the Pooled Cohort Equations both overestimate the risk of cardiovascular events. Over 12 years, no association between egg consumption and cardiovascular events was demonstrated. Gabapentin, pregabalin, duloxetine, and venlafaxine provide clinically meaningful improvements in chronic neuropathic pain. In patients with moderate to severe depression, initial titration above the minimum starting dose of antidepressants in the first eight weeks of treatment is not more likely to increase response. In adults with iron deficiency anemia, adding vitamin C to oral iron has no effect. In children with pharyngitis, rhinosinusitis, acute bronchitis, or acute otitis media, providing education combined with a take-and-hold antibiotic prescription results in 1 in 4 of those children eventually taking an antibiotic. (*Am Fam Physician*. 2022;online. Copyright © 2022 American Academy of Family Physicians.)

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Annually for 23 years, a team of clinicians has systematically reviewed English-language medical journals to identify the research most likely to change and improve primary care. The team includes experts in family medicine, pharmacology, hospital medicine, and women's health.[1,2]

The goal of this process is to identify POEMs (patient-oriented evidence that matters). A POEM must report at least one patient-oriented outcome, such as improvement in symptoms, morbidity, or mortality. It should also be free of important methodologic bias, making the results valid and trustworthy. Finally, if the results were applied in practice, some physicians would change what they do by adopting a new practice or discontinuing an old one shown to be ineffective or harmful. Adopting POEMs in clinical practice should improve patient outcomes. Of more than 20,000 research studies published in 2021 in the journals reviewed by the POEMs

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TABLE 2

Musculoskeletal Conditions

(5) acetaminophen, 325 mg, with oxycodone, 5 mg. Pain scores decreased by about 3 points on a 10-point scale in all ve groups at one hour and by about 4.5 points at two hours, with no signi cant di erence between groups. About 1 out of 4 patients in each group required rescue pain medication, again with no di erence. Nausea and vomiting were more common in patients receiving an opioid. us, a good choice is acetaminophen, 1,000 mg, plus ibuprofen, 400 mg, or even acetaminophen alone, without an opioid.[15]

A large systematic review asked the question: Which nondrug therapies are e ective for chronic musculoskeletal pain?[14] For chronic low back pain, exercise, massage, yoga, cognitive behavior therapy, mindfulness-based stress reduction, acupuncture, spinal manipulation, low-level laser therapy, and rehabilitation all reduced pain and/or improved function. ere was evidence for the use of exercise, massage, low-level laser therapy, acupuncture, and Pilates in the treatment of chronic neck pain. Only exercise and cognitive behavior therapy were helpful for knee osteoarthritis. ere is evidence only for the use of exercise and manual therapies for the treatment of hip osteoarthritis. Patients with bromyalgia bene ted from cognitive behavior therapy, myofascial release massage, tai chi, qi gong, acupuncture, rehabilitation, and exercise.

Gastrointestinal

e next set of POEMs addresses colorectal cancer screening, constipation treatment, and vague abdominal symptoms (Table 3).[16-18] Most countries screen for colorectal cancer using fecal immunochemical testing (FIT) as the initial method. Canada includes exible sigmoidoscopy as an option, and the United States most commonly uses colonoscopy. e rst POEM on gastrointestinal conditions is a Norwegian RCT that invited previously unscreened adults 50 to 74 years of age to undergo exible sigmoidoscopy (52% had the procedure) or FIT every two years (68% had at least one test).[16] Although exible sigmoidoscopy initially identi ed more cancers and advanced adenomas, FIT surpassed it over time, with a cancer detection rate of 0.49% a er three rounds of FIT testing vs. 0.27% with exible sigmoidoscopy. is is a very important point screening programs must be compared over time, not just a er a single round, using di erent tests. RCTs comparing FIT with colonoscopy over time are underway.

In a systematic review of over-the-counter treatments for chronic constipation, polyethylene glycol (Miralax) and senna were the most e ective initial options.[17] Fiber supplements, other stimulant laxatives, magnesium-based products, and fruit-based products were also e ective.

e nal POEM evaluated the predictive value of common abdominal symptoms for cancer or in ammatory bowel disease.[18] Combinations of symptoms, such as change in bowel habits with rectal bleeding, were more predictive but varied by age and sex. Dysphagia or changes in bowel habits in men and rectal bleeding in women should prompt referral for further workup to exclude cancer or in ammatory bowel disease. Dyspepsia was largely unhelpful, except in patients older than 60 years. e severity and duration of gastrointestinal symptoms and whether they appear to be progressive were not part of this study but are important additional factors.

Cardiovascular Disease

Four POEMs about cardiovascular disease made the top 20 list (Table 4).[19-22] e rst two addressed prevention. One was a large pragmatic trial that randomized 15,076 patients with established arteriosclerotic cardiovascular disease to 81 mg or 325 mg of aspirin daily and evaluated the likelihood of death, nonfatal myocardial infarction, or nonfatal stroke a er a median of two years.[19] ere was no di erence between groups for these outcomes (7.3% for 81 mg and 7.5% for 325 mg) and no di erence in hospitalization for major bleeding. e trial was a bit messy, with 7% in the 81-mg group switching to 325 mg and 42% in the 325-mg group switching to the lower dose. It is not clear why so many switched to the lower dose, but, for whatever reason, there is no advantage with the higher dose.

U.S. guidelines for cardiovascular prevention all begin with an assessment of cardiovascular risk using the Pooled Cohort Equations. e second cardiovascular POEM warns us that this score signi cantly overestimates risk. e Canadian researchers identi ed more than 80,000 people 40 to 79 years of age and estimated their risk using the Framingham Risk Score and the Pooled Cohort Equations.[20] Cardiovascular risk estimates from both tools were about twice as high as the real-world risk. e overestimates occurred in all groups regardless of age and sex but

TABLE 3

Gastrointestinal Conditions

TABLE 4

Cardiovascular Diseases

Clinical question	Bottom-line answer
13. What dose of aspirin is best for secondary prevention in people with established ASCVD?[19]	**The best daily dosage of aspirin to use for secondary prevention of ASCVD is 81 mg.** There is no advantage to using a 325-mg dose of aspirin for patients with established ASCVD, and people taking the higher dose often switch to the lower dose (although the reason is unclear).
14. How well do the Framingham Risk Score and Pooled Cohort Equations estimate the risk of cardiovascular events in the general population?[20]	**These two commonly used cardiovascular risk scores overestimate the risk of cardiovascular events by about double.** The Framingham Risk Score and Pooled Cohort Equations both significantly overpredicted the five-year risk of a composite cardiovascular event outcome. This is consistent with other research and should give us pause as we use these risk scores to guide therapeutic decision-making. For example, a person with a 10-year risk of 10% probably has a true risk closer to 5%, leading to very different guideline recommendations for a statin.
15. How do routine clinical measurements of systolic blood pressure compare with ideal blood pressure measurement?[21]	**Office measurements tend to overestimate "true" blood pressure.** Compared with blood pressure measurements that follow the strict protocols used in research, measurement in typical physician offices will be an average of 4.6 to 7.3 mm Hg higher for systolic readings. This study also found wide variations in clinical blood pressure readings compared with the reference standard. SPRINT demonstrated that reducing a systolic blood pressure to less than 120 mm Hg is associated with decreased mortality. However, most guidelines suggest higher goals, given that the SPRINT method of blood pressure measurement was more accurate than the method used in usual clinical practice, which overestimates true blood pressure.
16. Is the consumption of eggs associated with an increased risk of cardiovascular disease?[22]	**Eggs do not increase the risk of cardiovascular disease.** Over an average of 12 years, egg consumption is not associated with increased cardiovascular events. This meta-analysis showed that eating more than one egg per day, on average, was associated with an approximately 11% decreased likelihood of coronary artery disease. However, this decrease may be due to a healthy user bias (i.e., eating eggs might be associated with healthier habits).

ASCVD = arteriosclerotic cardiovascular disease; SPRINT = Systolic Blood Pressure Intervention Trial.

Information from references 19-22.

tended to be larger in younger patients. This is important for shared decision-making. For example, an estimated risk of 10% based on the Pooled Cohort Equations might lead to prescribing a statin, but the true cardiovascular risk may be significantly lower.

The U.S. Preventive Services Task Force draft guidelines recommend prescribing a statin for adults 40 to 75 years of age with at least one cardiovascular risk factor (dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year cardiovascular risk of 10% or greater. Statins should be selectively offered to those with a risk factor and a risk between 7.5% and 10% because the benefits are smaller than those at higher risk.[23]

Another calibration issue was addressed by the third POEM. The researchers compared the blood pressure measurements used by researchers in SPRINT (Systolic Blood Pressure Intervention Trial) with those recorded by the patients' regular primary care physicians.[21] The physician-recorded systolic blood pressure measurements were about 5 to 7 mm Hg higher; therefore, the SPRINT recommendations to lower systolic blood pressure to less than 120 mm Hg need to be interpreted accordingly—in the real world, achieving a level of 130 mm Hg is probably similar to 120 mm Hg in the trial setting.

The next POEM made our day, as egg lovers. This systematic review included 23 observational studies with nearly 1.4 million patients.[22] Eating more eggs was not shown to increase the risk of cardiovascular events. In fact, compared with eating one or no eggs per day, those eating more than one egg per day had a decreased risk of coronary disease (hazard ratio = 0.89; 95% CI, 0.86 to 0.93).

Miscellaneous

Four top POEMs do not fall easily into a single category *(Table 5)*.[24-27] A systematic review addressed treatment of chronic pain caused by diabetic neuropathy or postherpetic neuralgia.[24] It included only studies reporting an outcome of clinically meaningful response, defined as a 30% improvement on a pain or function score. Moderate-quality evidence supported the use of the anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica) and the serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine, and low-quality evidence supported the use of rubefacients (usually salicylates). The NNT was 7 or 8 for all the identified therapies. Opioid studies were of low quality and also showed more harms (number needed to harm = 12). Only a few trials with low-certainty evidence studied acupuncture and tricyclic antidepressants.

A systematic review identified RCTs that compared treatment of moderate to severe depression using the minimum licensed dose of a selective serotonin reuptake inhibitor, venlafaxine, or mirtazapine (Remeron) with a dosing regimen that allowed titration to higher doses.[25] There was no improvement in the balance of effectiveness and harms between taking the minimum dose and titrating to higher doses, although patients taking venlafaxine may respond to a higher dose if they show no response to the minimum dose.

The next POEM identified 436 children with pharyngitis, rhinosinusitis, acute bronchitis, or acute otitis media whose treating physician had reasonable doubts about the need for an antibiotic.[26] Patients were randomized to no antibiotics; an immediate antibiotic; or an antibiotic prescription to be filled only if the child had fever, felt much worse after 24 hours, or was not improving after a longer period (varied by type of infection). Only 25% of children in the delayed antibiotic group and 12% in the no antibiotic group ultimately filled a prescription, and there was no difference between these groups and the immediate antibiotic group in the duration of symptoms (eight days) or complications. Gastrointestinal symptoms and cost were higher in those receiving an antibiotic.

TABLE 5

Miscellaneous

Clinical question	Bottom-line answer
17. Which treatments for chronic neuropathic pain can provide clinically meaningful improvement?[24]	**The anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica) and the SNRIs duloxetine (Cymbalta) and venlafaxine improve chronic neuropathic pain.** Given the balance of benefits and harms, there is moderate-quality evidence for anticonvulsants (gabapentin and pregabalin were similarly effective and well tolerated) and SNRIs (duloxetine and venlafaxine were similarly effective and well tolerated). Rubefacients (usually salicylates) appear to be effective but are not as well studied and have low-quality evidence. Acupuncture, opioids, and tricyclic antidepressants cannot be recommended based on current evidence.
18. Does increasing antidepressants to above the minimum dose improve outcomes?[25]	**Low doses of selected antidepressants work just as well as higher doses.** For new-generation antidepressants, including selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine (Remeron), initial titration over the first eight weeks of treatment provides no benefit over starting with the minimum dose in patients with moderate to severe depression. Unfortunately, this means waiting six to eight weeks to judge the response to treatment before moving to another medication.
19. What is the effect of a delayed prescription approach for children with respiratory tract infection?[26]	**"Take-and-hold" prescriptions for upper respiratory tract infections reduce antibiotic use and adverse effects.** A strategy of providing education about the natural history of respiratory symptoms in children combined with giving a take-and-hold prescription (to be filled only if symptoms persist) resulted in only 1 in 4 children eventually taking an antibiotic. However, it increased the number of children who used other medications to control symptoms, which indicates the parents' need to do something. Symptom severity and time to resolution, complications, and follow-up visits were similar whether children received immediate, delayed, or no antibiotic treatment. Immediate treatment resulted in more gastrointestinal symptoms. Similar results have been shown in adults.
20. Is supplemental oral vitamin C plus iron replacement more effective than oral iron replacement alone in adults with iron deficiency anemia?[27]	**Vitamin C should not be added to iron replacement therapy.** This study found no difference in hemoglobin or serum ferritin level after three months in adults with iron deficiency anemia who were treated with oral iron plus vitamin C vs. oral iron alone.

SNRI = serotonin-norepinephrine reuptake inhibitor.

Information from references 24-27.

TABLE 6

Practice Guidelines

Clinical question	Bottom-line answer
21. Are short antibiotic courses as effective as longer courses for common infections?[28]	**Short antibiotic courses should be used for community-acquired pneumonia, COPD exacerbation, uncomplicated pyelonephritis, and nonpurulent cellulitis.** American College of Physicians guidelines recommend five days of antibiotics for community-acquired pneumonia, five days for COPD exacerbation, five to seven days for uncomplicated pyelonephritis if using a quinolone, and five to six days for nonpurulent cellulitis. Longer courses may be necessary if there is no clinical improvement. Guideline summary: https://www.aafp.org/afp/2022/0200/p205.html
22. What therapies are recommended for acute pain from non–low back musculoskeletal injuries?[29]	**Topical NSAIDs are first-line therapy for non–low back musculoskeletal injuries. Oral NSAIDs, acetaminophen, acupressure, or TENS may also be used.** The American College of Physicians and American Academy of Family Physicians collaborated to create guidelines on the management of non–low back musculoskeletal injuries. Based on a large systematic review and network meta-analysis, they give a strong recommendation for topical diclofenac as first-line therapy and a conditional recommendation for oral NSAIDs, acetaminophen, acupressure, or TENS. Opioids are not recommended because of greater adverse effects and risk of prolonged use. Guideline summary: https://www.aafp.org/afp/2020/1201/p697.html
23. What is the optimal approach to screening for tobacco use in adults?[30]	**Physicians should screen for tobacco use in all adults and provide behavioral interventions and pharmacotherapy to aid in smoking cessation.** The U.S. Preventive Services Task Force found sufficient evidence to support the use of nicotine replacement therapy, bupropion, varenicline (Chantix), or behavioral interventions, with the combination of pharmacotherapy and behavioral interventions more effective than either alone. Effective behavioral interventions include advice from a physician or nurse, individual counseling, group behavioral interventions, telephone counseling, mobile phone–based interventions (including texting), health education, feedback, financial incentives, and social support. In pregnancy, only behavioral interventions are recommended given the lack of evidence around pharmacotherapy in pregnancy. Guideline summary: https://www.aafp.org/afp/2021/0615/od1.html

COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti-inflammatory drug; TENS = transcutaneous electrical nerve stimulation.

Information from references 28-30.

Finally, clinicians have long recommended that people taking iron supplements also take vitamin C because it theoretically improves absorption. A study tested the theory by randomizing 440 adults with iron deficiency anemia to ferrous succinate, 100 mg, plus vitamin C, 200 mg, or to ferrous succinate alone, each given every eight hours. There was no difference in hemoglobin or serum ferritin levels at three months.[27]

Practice Guidelines

POEMs sometimes summarize high-impact clinical practice guidelines. Key messages from the three highest-rated guidelines, which address antibiotics for common infections, non–low back musculoskeletal injuries, and tobacco screening and cessation, are summarized in *Table 6*.[28-30]

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