

Useful treatments for fibromyalgia syndrome

Goldenberg DL, Burchhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004; 292:2388–2395.

■ CLINICAL QUESTION

What treatment modalities are most effective for fibromyalgia syndrome?

■ BOTTOM LINE

Treatments for fibromyalgia syndrome with the strongest evidence for efficacy include amitriptyline (Elavil), cyclobenzaprine (Flexeril), exercise, cognitive behavioral therapy, patient education, and multidisciplinary therapy. (Level of evidence [LOE]=1a–)

■ STUDY DESIGN

Meta-analysis (other)

■ SETTING

Various (meta-analysis)

■ SYNOPSIS

The optimal method for treating fibromyalgia syndrome is unclear. The investigators thoroughly searched multiple sources—including Medline, EMBASE, Science Citation Index, and the Cochrane Collaboration—for trials evaluating the effectiveness of treatment for fibromyalgia syndrome. A total of 505 articles were reviewed and classified according to their level of evidence. The authors don't state whether the articles were reviewed independently and do not discuss the potential for publication bias.

Evidence was ranked as *strong* (positive results from a meta-analysis or consistent results from more than 1 randomized controlled trial [RCT]),

moderate (positive results from 1 RCT or mostly positive results from multiple RCTs or consistently positive results from non-RCT studies), or *weak* (positive results from descriptive and case studies, inconsistent results from RCTs, or both).

Strong evidence for efficacy was found for treatment with amitriptyline, cyclobenzaprine, exercise, cognitive behavioral therapy, and patient education. Modest evidence for efficacy was found for tramadol (Ultram), various selective serotonin reuptake inhibitors, acupuncture, hypnotherapy, and biofeedback. Weak evidence for efficacy was found for growth hormone therapy, SAM (S-adenosyl-methionine), chiropractic and massage therapy, electrotherapy, and ultrasound. No evidence of any evaluation or effectiveness was found for steroids, nonsteroidal anti-inflammatory drugs, melatonin, benzodiazepine hypnotics, or trigger-point injections.

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Bottom Line observation and summarizes the study's objective, patient population, study design and validity, and results. InfoPOEMs, Info-Retriever and POEMs for Primary Care are registered trademarks of InfoPOEM, Inc. POEMs and Patient-Oriented Evidence that Matters are trademarks of InfoPOEM, Inc. These POEMs are copyrighted by, and published with the express permission of InfoPOEM, Inc. and may not be copied or otherwise reproduced without the prior written consent of InfoPOEM, Inc.

Tight blood pressure control prevents blindness in patients with diabetes

UK Prospective Diabetes Study Group. Risks of progression of retinopathy and vision loss related to tight blood pressure control in Type 2 diabetes mellitus. *Arch Ophthalmol* 2004; 122:1631–1640.

■ CLINICAL QUESTION

Does tight blood pressure control improve visual outcomes in diabetic hypertensive patients?

■ BOTTOM LINE

Tight blood pressure control results in a small benefit in the prevention of blindness, with a number needed to treat of 1000 per year. Tight control was also associated with a reduction in loss of visual acuity after 9 years (but not with shorter durations of follow-up) and an increase in the likelihood of cataract extraction. (LOE=1b)

■ STUDY DESIGN

Randomized controlled trial (double-blinded)

■ ALLOCATION

Concealed

■ SETTING

Outpatient (any)

■ SYNOPSIS

This is yet another report from the landmark United Kingdom Prospective Diabetes Study (UKPDS) of patients with type 2 diabetes. In this substudy, 1148 hypertensive patients with diabetes were randomly assigned in a 2:1 ratio to tight or loose control of blood pressure, with target blood pressures of 150/85 mm Hg or 200/105 mm Hg, respectively. The loose control target was changed to 185/105 mm Hg midway through the study.

Patients in the active treatment group were further randomized to receive either captopril

(Capoten) or atenolol (Tenormin) in standard doses, increased until control was achieved, with furosemide (Lasix), nifedipine (Procardia), methyldopa (Aldomet), or prazosin (Minipres) added (in that order), if needed. The degree of retinopathy was evaluated at enrollment and every 3 years thereafter. Allocation to groups was concealed, outcome assessment was blinded, and analysis was by intention to treat.

Patients were followed for a median of 9.3 years. The average blood pressure in the tight control group was 144/82 mm Hg and in the loose control group was 154/87 mm Hg. The mean glycohemoglobins were similar in these groups: 7.2% during the first 4 years of the study, and 8.2% to 8.3% for the final 4 years. The tight control group had fewer microaneurysms after 4.5 years follow-up (23.3% vs 33.5%; number needed to treat [NNT]=10), fewer hard exudates, fewer cotton-wool spots, less progression of retinopathy, and less need for photocoagulation. These are all disease-oriented endpoints and do not necessarily result in significant worsening of vision or visual loss.

The primary patient-oriented outcomes are blindness and reduction in visual acuity. Visual loss in one eye was less likely in the tight control group, occurring in 2.4% of patients in the tight control group compared with 3.1% in the loose control group ($P=.046$). This corresponds to an absolute increase in risk with loose control of approximately 1 per 1000 patient-years of treatment. After 9 years, there was a lower likelihood of deterioration in either eye in the tight control group (20.5% vs 32.8%; NNT=8). However, there was no significant difference in the reduction of vision as assessed by the better eye.

An interesting finding, not otherwise commented on in the manuscript, was that 36 patients in the tight control group required cataract extraction compared with only 14 in the loose control group. We are not given the statistical significance of this difference, but judging by the other differences it almost certainly was significant.

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Evidence-based medicine ratings

THE JOURNAL OF FAMILY PRACTICE uses a simplified rating system system called the Strength of Recommendation Taxonomy (SORT). More detailed information can be found in the February 2003 issue, "Simplifying the language of patient care," pages 111–120.

Strength of Recommendation (SOR) ratings are given for key recommendations for readers. SORs should be based on the highest-quality evidence available.

- A** Recommendation based on consistent and good-quality patient-oriented evidence.
- B** Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C** Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

Levels of evidence determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies.

STUDY QUALITY

- 1**—Good-quality, patient-oriented evidence (eg, validated clinical decision rules, systematic reviews and meta-analyses of randomized controlled trials [RCTs] with consistent results, high-quality RCTs, or diagnostic cohort studies)
- 2**—Lower-quality patient-oriented evidence (eg, unvalidated clinical decision rules, lower-quality clinical trials, retrospective cohort studies, case control studies, case series)
- 3**—Other evidence (eg, consensus guidelines, usual practice, opinion, case series for studies of diagnosis, treatment, prevention, or screening)

Consistency across studies

Consistent—Most studies found similar or at least coherent conclusions (coherence means that differences are explainable); *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation

Inconsistent—Considerable variation among study findings and lack of coherence; *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

ARB no better than ACE inhibitor for prevention of nephropathy progression

Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351:1952–1961.

CLINICAL QUESTION

Are angiotensin receptor blockers as good as angiotensin-converting enzyme inhibitors at preventing the progression of nephropathy?

BOTTOM LINE

Despite a relatively low dose of 10 mg given once a day, enalapril (Vasotec) was at least as effective as telmisartan (Micardis) and showed a trend toward greater benefit in preventing decline in glomerular filtration rate. Although this study measured a disease-oriented endpoint, its results are consistent with the body of literature that supports the less expensive angiotensin-converting enzyme (ACE) inhibitors as the drug of choice over angiotensin receptor blockers (ARBs). (LOE=1b)

STUDY DESIGN

Randomized controlled trial (double-blinded)

ALLOCATION

Uncertain

SETTING

Outpatient (any)

SYNOPSIS

This study is what we call DOE (disease-oriented evidence), since it measured progression of nephropathy instead of the patient-oriented outcome of renal failure or need for dialysis. However, the results are worth knowing because we so often hear of the potential DOE-related advantages of ARBs over the older, less expensive, and less often promoted ACE inhibitors.

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In this study, 250 subjects with diabetes and mild to moderate hypertension and evidence of early nephropathy (urinary albumin excretion rate between 11 and 999 µg/minute and a serum creatinine less than 1.6 mg/dL) were randomized to receive either telmisartan 40 mg/d or enalapril 10 mg/d. Blood pressure medicines other than an ACE inhibitor or ARB could be added at the discretion of the treating physician to control blood pressure. The primary outcome was the glomerular filtration rate. There was a high dropout rate, and the last observation was appropriately carried forward for the analysis. The results for only those patients with complete data were also reported. In both cases, there was almost no difference in glomerular filtration rate for the first 2 years, with a trend toward greater benefit for enalapril that almost became significant at 4 years and declined slightly at 5 years.

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Adding ACE inhibitor doesn't improve outcomes in stable angina and normal LVEF

PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004; 351:2058–2068.

■ CLINICAL QUESTION

Does adding an angiotensin-converting enzyme inhibitor improve outcomes among patients with stable angina and no evidence of heart failure?

■ BOTTOM LINE

Adding the angiotensin-converting enzyme (ACE) inhibitor trandolapril (Mavik) to standard medical treatment of patients with stable angina and normal left ventricular function did not reduce their risk of adverse cardiovascular outcomes. Although higher-risk patients and those with less well controlled risk factors may still benefit from this intervention, this study didn't assess those groups. (LOE=1b)

■ STUDY DESIGN

Randomized controlled trial (double-blinded)

■ ALLOCATION

Concealed

■ SETTING

Outpatient (any)

■ SYNOPSIS

The HOPE and EUROPA trials found that ACE inhibitors improve cardiovascular outcomes in patients with vascular disease but with no evidence of overt heart failure. This study attempted to extend these findings to an even lower-risk group using the ACE inhibitor trandolapril (Mavik). The researchers recruited patients older than 50 years with documented coronary artery disease and a left ventricular ejection fraction (LVEF) >40%, excluding patients in poor health, with renal failure, recent unstable angina, or who had recently used an ACE inhibitor. Only patients who tolerated the active drug during a run-in phase were allowed into the study, a step that increases the likelihood of finding a benefit for the drug. The mean age of participants was 65 years, 18% were women, 55% had had a myocardial infarction (MI), 92% were white, and 17% had diabetes. Patients were randomized (allocation concealed) to trandolapril 2 mg per day, increased to 4 mg per day if tolerated, or matching placebo.

Outcomes were blindly assessed and analysis was by intention to treat. The primary outcome began as death or nonfatal MI, but was expanded to include coronary revascularization as a way to reduce sample size and save money halfway through the study. The final sample included 4158 in the trandolapril group and 4132 in the placebo group; patients were followed for a median of 4.8 years. During the study, the safety monitoring committee recommended that all diabetic patients with microalbuminuria be given an ACE inhibitor, effectively removing them from the study. Removing data for these patients did not affect the overall study results.

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Much to the investigators' surprise, there was no difference between groups regarding the primary outcome (21.9% in the trandolapril group vs 22.5% in the placebo group) at the end of the study. They hypothesize that this is due to the lower overall risk of the patients in the PEACE study compared with those in the HOPE and EUROPA trials. Certainly, when patients are at greater risk of bad outcomes, they tend to benefit more from interventions, so this argument may have merit. Another explanation is that trandolapril is less effective than ramipril (HOPE) or perindopril (EUROPA), although the extent of blood pressure lowering (3 mm) was similar to that in the HOPE and EUROPA studies.

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Cost-effective management for nephrolithiasis

Lotan Y, Cadeddu JA, Roerhborn CG, Pak CY, Pearle MS. Cost-effectiveness of medical management strategies for nephrolithiasis. *J Urology* 2004; 172:2275–2281.

■ CLINICAL QUESTION

What are the most cost-effective treatment strategies for the medical management of patients with kidney stones?

■ BOTTOM LINE

For patients with first-time kidney stones, conservative therapy (dietary modification only) is the most cost-effective strategy. In recurrent stone formers, both empiric therapy (dietary modification and potassium citrate) and a modified simple metabolic evaluation (one 24-hour urine collection for renal stone risk factors, with both potassium citrate and hydrochlorothiazide for patients with hypercalciuria and potassium citrate alone for patients with normocalciuria) are equally cost-effective. (LOE=2b)

■ STUDY DESIGN

Cost-effectiveness analysis

■ SETTING

Population-based

■ SYNOPSIS

These investigators constructed a decision tree to estimate the cost of treatment and follow-up in patients with calcium oxalate renal stones. They searched the medical literature using Medline to identify studies addressing the natural history, evaluation, and medical and surgical treatment of nephrolithiasis. Costs of various outcomes were estimated using the authors local (Dallas, Tex) hospital and pharmacy charges from 2 national chains for specified diagnostic tests, medications, and surgical procedures.

Six strategies were evaluated: (1) *conservative therapy*: dietary modification without drug treatment or metabolic evaluation; (2) *empiric medical therapy*: dietary modification and drug treatment (potassium citrate) for all patients; (3) *modified simple metabolic evaluation*: a single 24-hour urine collection for analysis of common urinary stone risk factors, with both potassium citrate and hydrochlorothiazide prescribed for patients with hypercalciuria, and potassium citrate alone for patients with normocalciuria; (4) *simple metabolic evaluation*: same evaluation as #3, except that patients with normocalciuria and no other identifiable abnormality receive no drug therapy; (5) *modified comprehensive metabolic evaluation*: at least two 24-hour urine collections for stone risk analysis and a fasting oral calcium load test with similar treatment as in #3; and (6) *comprehensive metabolic evaluation*: same workup as #5, but with treatment only for patients with an identified disorder.

A sensitivity analysis evaluated medication cost thresholds at varying levels of risk that would achieve cost equivalence with conservative (diet only) therapy for each treatment strategy. In first-time stone formers, conservative therapy was the most cost-effective strategy. In recurrent stone formers, both empiric therapy and the modified simple metabolic evaluation were equally the most cost-effective strategies.

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