

Physical therapy adds little to back pain treatment

Clinical question Do patients with back pain who undergo physical therapy benefit more than those simply given advice to remain active?

Bottom line Physical therapy sessions do not offer any additional benefit over simple advice to remain active in patients referred for physical therapy. Patients will initially perceive a benefit while being treated, but this benefit disappears by 1 year. (Level of evidence = 2b)

Frost H, Lamb SE, Doll HA, et al. Randomised controlled trial of physiotherapy compared with advice for low back pain. *BMJ*. 2004;329:708-11.

Study Design Randomized controlled trial (single-blinded)

Allocation Concealed

Setting Outpatient (specialty)

Synopsis The authors of this study started with 286 patients with low back pain in the United Kingdom who were referred by their general practitioner or specialist for physical therapy. The patients were invited to participate in the study and were randomized (allocation assignment was concealed) to receive either an advice booklet from a physical therapist to remain active or the book plus 6 treatment sessions of physical therapy using joint mobilization and manipulation, soft tissue techniques, and strengthening exercises. Analysis was by intention to treat, although follow-up after 1 year was only 70%. The main outcome was the change in the Oswestry disability index, a scale completed by patients that has a range from 0% (no disability) to 100% (totally disabled). There was no difference in disability 1 year after treatment assignment. Quality of life scores were not different at 1 year as measured by the 36-item Short-Form Health Status Survey. Approximately 10% of patients randomized to receive advice only received physical therapy. Patients reported significantly more benefit from treatment at both 2 and 6 months, but it's likely—given that patients were aware of their treatment—that this finding reflects a placebo effect. Other research has also not shown a benefit of physical therapy for low back pain (*Spine*. 2003;13:1363-72).

ACE inhibitors beneficial in diabetics

Clinical question Are ACE inhibitors or angiotensin receptor blockers beneficial in patients with diabetes who have microalbuminuria or macroalbuminuria?

Bottom line Treatment with an angiotensin converting enzyme inhibitor, but not angiotensin receptor blockers, delays mortality in patients with diabetes who also have microalbuminuria (and pre-existing heart disease) or frank albuminuria. This benefit occurs regardless of whether patients were also hypertensive. Angiotensin receptor blockers have been demonstrated to prevent a decline in renal function and decrease the likelihood of end-stage renal disease in high-risk patients. This analysis does not provide good evidence that screening for and treating microalbuminuria in patients with diabetes but without heart disease is effective. (Level of evidence = 1a)

Strippoli GF, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ*. 2004;329:828.

Study Design Meta-analysis (randomized controlled trials)

Setting Outpatient (any)

Synopsis Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are recommended for use in patients with diabetes with either microalbuminuria or frank albuminuria, regardless of blood pressure status. This meta-analysis summarized the current

data on the effectiveness of these drugs in preventing overall mortality and end-stage renal disease, reducing the likelihood of a decline in renal function, and, less important, the progression from microalbuminuria to frank albuminuria. The investigators searched several databases using Cochrane Collaboration search strategies. Study selection, data extraction, and quality assessment were performed in the usual manner. They ended up with 43 randomized studies enrolling 7545 patients. Most of the research compares an ACE inhibitor with placebo in patients with microalbuminuria and pre-existing heart disease (the Micro-HOPE study). Treatment with an ACE inhibitor decreases overall mortality (8.50% versus 12.12%). The number needed to treat is 44 for approximately 4.5 years, though the range is very large (95% CI, 24.2 - 938). ARBs, studied on similar numbers of patients but for shorter time periods, have not shown any effect on mortality. ACE inhibitors do not decrease the development of end-stage renal disease, although the rate was low to begin with (4.3%) in the studied patients. ARBs have been demonstrated to have an effect in patients at high risk (19.3%) of developing end-stage renal disease. Similarly, ARBs, but not ACE inhibitors, have been demonstrated to have an effect on progression of renal disease as measured by the doubling of serum creatinine. Both types of drugs decrease the number of patients with microalbuminuria who progress to macroalbuminuria, although the significance of this outcome is not known. There is not enough research that directly compares the two types of drugs to provide guidance regarding which is better.

Lamivudine slows progression in Hep B with advanced fibrosis

Clinical question Is lamivudine safe and effective for the treatment of hepatitis B in patients with advanced liver disease?

Bottom line For every 10 patients with chronic hepatitis B and advanced liver disease who take lamivudine instead of placebo for 2.5 years, 1 fewer patient experiences progression of their liver disease. Long-term use of lamivudine often triggers the YMDD mutation, and the benefit is attenuated in these patients. (Level of evidence = 1b)

Liaw Y-F, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521-31.

Study Design Randomized controlled trial (double-blinded)

Allocation Uncertain

Setting Outpatient (specialty)

Synopsis Lamivudine is an oral antiviral agent that is less expensive and somewhat better tolerated than interferon. This study identified adults with chronic hepatitis B who were HBeAg positive or HBeAg negative with detectable hepatitis B virus DNA and who had histologic evidence of advanced liver fibrosis (Ishak fibrosis score of 4 or more on a scale of 0 to 6). Exclusion criteria included hepatocellular carcinoma, serum alanine aminotransferase more than 10 times the upper limit of normal, hepatic failure, autoimmune hepatitis, coinfection with hepatitis C or human immunodeficiency virus, anemia, leukopenia, and thrombocytopenia. Allocation appears to have been concealed via a central randomization process (although no details are given), and analysis was by intention to treat. Outcomes were assessed by a committee masked to treatment assignment. Most of the patients were male (85%) and almost all were Asian. Participants were randomized to either lamivudine, 100 mg per day (n=436), or placebo (n=215) and were supposed to be followed up for 5 years. However, the study was stopped prematurely once the benefit of lamivudine became apparent. The primary endpoint

was a combined outcome called "time to disease progression" and included an increase in the Child-Pugh score of 2 or more points, spontaneous bacterial peritonitis with sepsis, renal insufficiency, variceal bleeding, hepatocellular carcinoma, or death due to liver disease. After a median duration of treatment of 32 months, 34 of 436 patients in the lamivudine group and 38 of 215 patients in the placebo group had reached the primary combined endpoint (7.8% versus 17.7%; $P = .001$; absolute risk reduction 9.9%; number needed to treat [NNT] = 10). Most of the benefit was due to fewer patients with an increased Child-Pugh score (3.4% versus 8.8%; $P = .02$; NNT = 18) and fewer cases of hepatocellular carcinoma (3.9% versus 7.4%; $P = .05$; NNT = 29). After reaching an endpoint, patients had the option of receiving lamivudine during an open-label continuation phase of the study. During the double-blind phase, there were 2 deaths in the lamivudine group and none in the placebo group. Serious adverse events were similar between groups (12% for lamivudine vs 18% for placebo; $P = .09$). However, when the open label phase of the trial is included, there were actually more deaths in the lamivudine group (12 vs 4; statistical significance not reported). Approximately half of the patients in the lamivudine group developed the YMDD mutation during treatment, thought to be caused by lamivudine. These patients were more likely to reach the primary endpoint than those who remained negative (11% versus 4%) and were more likely to die of hepatocellular carcinoma, but they still did better than those receiving placebo.

Optimal oral antiplatelet therapy for vascular disease

Clinical question Which antiplatelet agents, used alone or in combination, are effective in preventing recurrent vascular events?

Bottom line Aspirin is the recommended oral first-line antiplatelet therapy for patients with ST-segment elevation myocardial infarction. Aspirin or clopidogrel is recommended for those with initial transient ischemic attack (TIA)/ischemic stroke; chronic stable angina; or peripheral arterial disease; and aspirin plus clopidogrel should be used for those with non-ST-segment elevation acute coronary syndrome. For second-line therapy, the combination of aspirin and clopidogrel is recommended for recurrent acute coronary syndrome. The combination of aspirin and extended-release dipyridamole is recommended for patients with recurrent TIA/ischemic stroke in the absence of known coronary artery disease. Further studies are needed before making firm recommendations on the management of patients with recurrent TIA/ischemic stroke and known coronary artery disease. (Level of evidence = 1a)

Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *JAMA*. 2004;292:1867-74.

Study Design Systematic review

Setting Various (meta-analysis)

Synopsis Aspirin prevents recurrent vascular events in a wide range of high-risk patients, but it is unknown if other antiplatelet agents, such as clopidogrel or dipyridamole, alone or in combination with aspirin, are more effective. The investigators rigorously searched multiple databases including MEDLINE, the Cochrane Clinical Trials Registry, and reference lists of trials, review articles, and scientific statements and guidelines of official societies. The authors included randomized trials comparing an antiplatelet regimen to either placebo or another antiplatelet regimen assessing outcomes for at least 10 days. They identified 111 trials enrolling nearly 100,000 patients. The investigators do not state if the search

for, and evaluation of, the included studies was done independently by more than one person. No formal assessment of the potential for publication bias was done, nor was any specific analysis done to determine homogeneity of the results. Recommended oral first-line antiplatelet therapy is aspirin for patients with ST-segment elevation myocardial infarction; aspirin or clopidogrel for those with initial transient ischemic attack (TIA)/ischemic stroke, chronic stable angina, or peripheral arterial disease (since aspirin is less expensive, clopidogrel should be reserved only for aspirin-intolerant patients); and aspirin plus clopidogrel for those with non-ST-segment elevation acute coronary syndrome. For second-line therapy, the combination of aspirin and clopidogrel is recommended for recurrent acute coronary syndrome. The combination of aspirin and clopidogrel does not, however, lower the incidence of recurrent vascular events in patients with recurrent TIAs/ischemic stroke but does increase the risk of major and life-threatening bleeding. The combination of aspirin and extended-release dipyridamole is therefore recommended for patients with recurrent TIA/ischemic stroke in the absence of known coronary artery disease. Because of the theoretical risk of dipyridamole exacerbating myocardial ischemia, further studies are needed before making firm recommendations on the management of patients with both recurrent TIA/ischemic stroke and known coronary artery disease. Ticlopidine is beneficial for various vascular conditions, but frequent side effects—some serious—limit its usefulness.

Ductal lavage ineffective in finding breast cancer

Clinical question Is ductal lavage effective in detecting breast cancer?

Bottom line In this small study, ductal lavage is an insensitive test for detecting breast cancer. (Level of evidence = 2b)

Khan SA, Wiley EL, Rodriguez N, et al. Ductal lavage findings in women with known breast cancer undergoing mastectomy. *J Natl Cancer Inst* 2004; 96:1510-17.

Study Design Cross-sectional

Setting Inpatient (any location)

Synopsis In the best of circumstances, screening mammography is only associated with a 30% reduction in breast cancer mortality. Because of this, researchers keep looking for a better test. Analogous to doing a Papanicolaou test of the breast, ductal lavage has been relatively unstudied beyond feasibility and acceptability. In this study, 32 women (mean age = 50 years) undergoing prophylactic ($n = 8$) or therapeutic mastectomy ($n = 35$) had ductal lavage performed in the operating room before surgery. The women were consecutively enrolled. To confirm that ducts were successfully lavaged, the surgeon injected a colored dye for the pathologist to identify. The authors don't report if the cytologists and pathologists were blinded to other test results. This study emphasized the analysis of 42 breasts. Two of the women undergoing prophylactic mastectomy had occult malignancies. At least one duct was successfully lavaged in 36 breasts, but only 31 yielded adequately cellular fluid. Cytology detected cancer in only 5 cancerous breasts. The ability of ductal lavage to find cancer in a breast is limited. Lavage only detected marked atypia 42% of the time and was accurate only half the time. Lowering the threshold so that mild atypia was also defined as abnormal lowered the overall accuracy and only detected 20% of the cancers. Since this is an extremely high-risk population, the sensitivity, even in high-risk women, will be even worse.

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