POEMs

Patient-Oriented Evidence That Matters

Relapse of Depression More Likely After Discontinuation of Medication

Clinical Question

For patients who are currently taking an antidepressant and are doing well, what is the likelihood of relapse after discontinuation of their medication?

Bottom Line

Primary care patients who discontinued antidepressant medications were more likely to experience relapse of their depression (number needed to harm [NNH] = 6) than those who continued to take their antidepressants. The interpretation is that 44% of patients with depression who discontinue their antidepressant medication when they are doing well continue to do well. (Level of Evidence = 1b–)

Synopsis

The researchers identified primary care patients who had at least two episodes of depression or had been taking antidepressants for at least two years. All patients felt well enough to consider discontinuing their medication; those with current depressive symptoms were excluded. The patients who had been taking citalopram (Celexa), 20 mg; fluoxetine (Prozac), 20 mg; sertraline (Zoloft), 100 mg; or mirtazapine (Remeron), 30 mg for at least nine months were randomized to continue their medication or discontinue their medication by substituting a placebo over a two month period. At baseline, the mean age of participants was 54 years, 73% were women, 95% were White, approximately one-half were taking citalopram, and approximately three-fourths had been taking an antidepressant for more than three years. The primary outcome was relapse of depression, defined as feeling sad, miserable, depressed, or being unable to enjoy or take an interest in things as much as usual, accompanied by at least one other depressive symptom for two weeks. After one year, this outcome occurred significantly more often in the placebo group (56% vs. 39%; hazard ratio = 2.06; 95% CI, 1.56 to 2.70; NNH = 6). Depression and anxiety symptoms were, on average, more severe in the discontinuation group. More patients in the discontinuation group stopped taking the placebo (48% vs. 30%; hazard ratio = 2.28; 95% CI, 1.68 to 3.08) and resumed antidepressant medications (39% vs. 20%). The mean scores on the 7-item Generalized Anxiety Disorder Questionnaire and the 9-question Patient Health Questionnaire were higher in the discontinuation group.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (primary care)

Reference: *Lewis G, Marston L, Duffy L, et al. Maintenance or discontinuation of antidepressants in primary care.* N Engl J Med. *2021;385(14):1257-1267.*

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Midodrine Is Worth a Trial in People With Frequent Episodes of Vasovagal Syncope

Clinical Question

Can midodrine decrease recurrent episodes of vasovagal syncope?

Bottom Line

Midodrine is a vasoconstrictor used to prevent orthostatic hypotension and may reduce the likelihood of recurrence of vasovagal syncope in patients with frequent episodes. It seems to work

completely or not at all; during this study, the patients who had at least one episode of syncope had several episodes over the course of the year regardless of whether they received midodrine or placebo. (Level of Evidence = 1b–)

Synopsis

The investigators enrolled 133 adults without orthostatic hypotension who had fainted at least twice (median = six times) in the past year and who did not have other known causes of syncope. Patients were randomized, concealed allocation unknown, to receive placebo or midodrine for one year. Treatment was started at 5 mg three times daily, during daylight hours, with the dosage increased up to 10 mg three times daily, if tolerated. Over one year, 58% of patients in the midodrine group were syncope-free compared with 39% in the placebo group (number needed to treat = 5). Midodrine was associated with a longer time to first recurrence of syncope ($P = .035$). In the subset of participants who had at least one syncope episode during the study, the rates were similar between treatments (i.e., 3.6 to 3.8 episodes per year).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry and government

Allocation: Uncertain

Setting: Outpatient (specialty)

Reference: *Sheldon R, Faris P, Tang A, et al.; POST 4 investigators. Midodrine for the prevention of vasovagal syncope: a randomized clinical trial.* Ann Intern Med. *2021;174(10):1349-1356.*

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Empagliflozin Reduces Hospitalization for Heart Failure With Preserved Ejection Fraction, but Not Mortality Outcomes

Clinical Question

Does empagliflozin (Jardiance), a sodium-glucose cotransporter-2 inhibitor, safely improve outcomes for patients who have heart failure with preserved ejection fraction?

Bottom Line

In patients who have heart failure with preserved ejection fraction, empagliflozin, 10 mg once daily, reduces the likelihood of hospitalization for heart failure (number needed to treat = 59 per year). There is no effect on cardiovascular or all-cause mortality. The drug costs $529 per month in the United States (www.goodrx.com; accessed October 30, 2021) and $82 per month in Canada (https://www.formulary.health.gov.on.ca/formulary; accessed October 30, 2021). In the United States, the drug is not cost-effective, and would require $375,000 to prevent one hospitalization; in Canada, that cost is $58,000. (Level of Evidence = 1b)

Synopsis

This industry-sponsored trial identified patients with New York Heart Association Class II through IV heart failure, an ejection fraction of at least 40%, and an N-terminal pro-brain natriuretic peptide (NT pro-BNP) level of more than 300 pg per mL (more than 900 pg per mL if the patient had atrial fibrillation). Of the 11,583 patients at 622 centers in 23 countries who were screened for the trial, 5,988 were randomized to receive empagliflozin, 10 mg once daily, or placebo. The primary reason for exclusion was failure to meet the NT pro-BNP target.

Groups were balanced at the beginning of the study, with a mean age of 72 years. Approximately one-third of patients in each group had ejection fractions of 40% to 50%, 50% to 60%, and 60% or higher, and 82% had Class II heart failure with preserved ejection fraction. Analysis was by intention to treat, with 77% of patients completing the trial and a median follow-up of 26 months. For the remainder of the patients, the trial medication was stopped for a reason other than death, presumably because of adverse events, although this was not specified by the authors.

The primary outcome was a composite of cardiovascular death or hospitalization due to heart failure. Hospitalization for heart failure occurred less often in patients randomized to receive empagliflozin (4.3 vs. 6.0 per 100 person-years; hazard ratio = 0.71; 95% CI, 0.60 to 0.83; number needed to treat = 59 per year). In an exploratory subgroup analysis, benefit was greater for those with lower ejection fractions. There was no significant difference in the likelihood of cardiovascular death (3.4 vs. 3.8 per 100 person-years) or all-cause mortality (6.6 vs. 6.7 per 100 person-years), and no significant differences in renal outcomes or hospitalization for any cause. There were 20 more noncardiovascular deaths in the

empagliflozin group, most often due to infection or sepsis, compared with 25 fewer cardiovascular deaths in that group. Hypotension and genital infections were more common in the empagliflozin group.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction.* N Engl J Med. *2021;385(16):1451-1461.*

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Platelet-Rich Plasma Injections Are Not Superior to Placebo Injections for Ankle Osteoarthritis

Clinical Question

Are platelet-rich plasma injections effective for alleviating pain and improving function in adults with symptomatic ankle osteoarthritis?

Bottom Line

This study found no evidence that supports a benefit of platelet-rich plasma injections compared with saline placebo injections for improving function or reducing pain in adults with symptomatic ankle osteoarthritis. (Level of Evidence = 1b)

Synopsis

There have been no published randomized trials evaluating the effectiveness of platelet-rich plasma injections for ankle osteoarthritis. The investigators identified 100 adults, 18 years or older, who presented to orthopedic and sports medicine outpatient clinics with a score of at least 40 for ankle pain severity on a visual analog scale (range = 0 to 100, where 100 is the most severe pain) and definitive radiographic evidence of tibiotalar osteoarthritis. Patients randomly received (concealed allocation assignment) two ultrasound-guided intra-articular injections of platelet-rich plasma six weeks apart (leukocyte poor; prepared with a widely used standard system) or matched saline as placebo. The patients also received lifestyle and exercise counseling. The individuals who assessed outcomes using a standard validated scoring tool for ankle osteoarthritis remained masked to treatment group assignment. Complete follow-up occurred for 100% of patients at 26 weeks. Using intention-to-treat analysis, mean improvement scores were similar in the platelet-rich plasma and placebo groups (10 vs. 11 points, respectively, on the American Orthopaedic Foot and Ankle Society scale of 0 to 100, where higher scores indicate improved function and reduced pain). No significant differences between groups occurred in any of the multiple secondary outcomes reported.

Study design: Randomized controlled trial (double-blinded)

Funding source: Foundation

Allocation: Concealed

Setting: Outpatient (specialty)

Reference: *Paget LDA, Reurink G, de Vos RJ, et al.; PRIMA Study Group. Effect of platelet-rich plasma injections vs placebo on ankle symptoms and function in patients with ankle osteoarthritis: a randomized clinical trial.* JAMA. *2021;326(16):1595-1605.*

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