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This series is coordinated by Sumi Sexton, MD, Associate Deputy Editor.

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Continuing Warfarin for 18 Months After Unprovoked PE Reduces Risk of Recurrent VTE

Clinical Question

Does continuing warfarin (Coumadin) for 18 months after an unprovoked pulmonary embolism (PE) reduce the risk of recurrent venous thrombotic events?

Bottom Line

Continuing warfarin therapy for 18 months after an unprovoked PE reduces the risk of recurrent symptomatic venous thromboembolism (VTE). However, benefit beyond 18 months is not maintained after the warfarin is discontinued. (Level of Evidence = 1b)

Synopsis

Patients with unprovoked VTE have a higher risk of recurrence than those with a provoked event. This is the first study to evaluate extended anticoagulation beyond six months for patients with unprovoked PE. The authors enrolled adults (N = 371), 18 years or older, who received six months of therapy with a vitamin K antagonist following their first episode of symptomatic unprovoked PE. Patients randomly continued to receive (concealed allocation assignment) warfarin (target international normalized ratio [INR] = 2 to 3) or placebo for 18 months. The investigators maintained double-blinding with the use of sham INR tests and results for the placebo group. Individuals who assessed outcomes remained masked to treatment group assignment.

Complete follow-up occurred for 97.8% of patients at 18 months and for 76.3% at 42 months.

Using intention-to-treat analysis, three of 184 patients in the warfarin group and 25 of 187 in the placebo group developed a symptomatic recurrent VTE during the 18-month treatment period (number needed to treat = 8.5; 95% confidence interval, 5.7 to 15.2). During the same period, four of 184 patients in the warfarin group and one of 187 patients in the placebo group experienced a major bleed (number needed to treat to harm = 61). After discontinuation of therapy at 18 months, the risk of symptomatic recurrent VTE in the warfarin group increased so that over the course of the entire study period (42 months) there was not a significant difference in the number of symptomatic recurrent VTEs between treatment groups. Thus, extending anticoagulation with warfarin beyond six months after an unprovoked VTE reduces the risk of recurrence, but only during the time of anticoagulation.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Inpatient (any location) with outpatient follow-up

Reference: Couturaud F, Sanchez O, Pernod G, et al.; PADIS-PE Investigators. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. *JAMA*. 2015;314(1):31-40.

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Gabapentin Equals Epidural Steroid for Radicular Pain

Clinical Question

Is an epidural steroid injection or gabapentin (Neurontin) more effective for pain relief in patients with lumbosacral radicular pain due to a herniated disk or spinal stenosis?

Bottom Line

After controlling for the placebo effect that may accompany an epidural steroid injection, treatment with gabapentin is as effective as the injection in reducing radicular leg pain in the short term (three months). A placebo bump in response, if present, is likely to be transient. (Level of Evidence = 1b) ▶

Synopsis

Patients enrolled in this study were recruited from eight hospitals in different areas of the United States and from a U.S. military facility in Europe. The 145 patients (74% men) had lumbosacral radicular pain due to a herniated disk or spinal stenosis for less than four years in duration, and the leg pain was as severe or more severe than back pain. The patients were randomly assigned, using concealed allocation, to receive gabapentin (titrated to between 1,800 and 3,600 mg per day in three doses for three months) or a single epidural injection of depo-methylprednisolone, 60 mg, with a local anesthetic. To mask patients to their treatment, thereby minimizing the placebo effect of the procedure or the daily medication use, all patients took daily medicine and all patients received an injection, with the patients in the gabapentin group receiving a saline injection. After one month, pain scores had decreased similarly in both groups. Patients receiving the steroid had a slightly better response to a reduction in their worst leg pain scores (a decrease of three points vs. two points; $P = .04$) and were more likely to report a positive successful outcome (number needed to treat = 5). By three months, though, improvement was similar in both groups.

Study design: Randomized controlled trial (double-blinded)

Funding source: Foundation

Allocation: Concealed

Setting: Outpatient (specialty)

Reference: Cohen SP, Hanling S, Bicket MC, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. *BMJ*. 2015;350:h1748.

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Citalopram Plus Methylphenidate Better Than Either Alone for Geriatric Depression

Clinical Question

What is the comparative effectiveness of citalopram (Celexa), methylphenidate (Ritalin), or both for the treatment of depression among older patients?

Bottom Line

Combined treatment with citalopram plus methylphenidate provided faster improvement of depression symptoms in older patients with unipolar depression. Combined treatment was also more likely than either medication alone to lead to remission of depression at

four weeks and 16 weeks. The study was too small to assess clinically meaningful differences in rare adverse drug effects. Because there was no dose-response effect with titration of the methylphenidate, a low dose (e.g., 5 mg twice daily) seems prudent. (Level of Evidence = 1b)

Synopsis

This randomized controlled trial of older patients with depression compared citalopram plus placebo (n = 48), methylphenidate plus placebo (n = 47), and both active treatments (n = 47). Inclusion criteria were unipolar depression by *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision criteria, a score of at least 16 on the Hamilton Depression Rating Scale (HAM-D), and a score of at least 22 on the Mini-Mental State Examination. Patients were excluded if they had severe or unstable medical illness, acute suicidal or violent behavior, a history of suicide attempts in the past year, any psychiatric diagnosis other than unipolar depression with or without comorbid anxiety, or other central nervous system diseases.

Methylphenidate (or placebo) was titrated during the first four weeks, as tolerated, starting at 2.5 mg twice daily and increasing to a maximum 20 mg twice daily. If response was insufficient at four weeks, citalopram (or placebo) was also increased from 20 to 40 mg or, in some cases, 60 mg daily. Remission rates were 30% among patients who received placebo instead of citalopram, 42% with 20 mg of citalopram, 56% with 40 mg, and 69% with 60 mg. There was no dose-response gradient with methylphenidate. Change in HAM-D score was greater and faster with combined therapy. Remission was defined as a HAM-D score of 6 or less and was more likely with combined therapy (62%) at 16 weeks, compared with citalopram alone (42%) or methylphenidate alone (29%; chi-squared test = 9.2; $P = .001$). There were no significant differences between groups in cognitive change, which improved across all groups. Note that the U.S. Food and Drug Administration currently recommends a 20-mg maximum daily dosage of citalopram.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (specialty)

Reference: Lavretsky H, Reinleib M, St Cyr N, Siddarth P, Ercoli LM, Senturk D. Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo controlled trial. *Am J Psychiatry*. 2015;172(6):561-569.

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