

Update in Neurology

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This Update in Neurology reviews important literature related to 6 main topics in the field: stroke, Parkinson disease, dementia, dizziness, epilepsy, and migraine headaches. The following papers represent the medical reports that have guided research during the past year.

Stroke

Mechanical Embolus Retrieval System Expanded the Window of Treatment Time in Acute Ischemic Stroke

Gobin YP, Starkman S, Duckwiler GR, et al. MERCI 1: a phase 1 study of Mechanical Embolus Removal in Cerebral Ischemia. *Stroke*. 2004;35:2848-54. [PMID: 15514171]

The Mechanical Embolus Removal in Cerebral Ischemia Retrieval System comprises a microcatheter and a retriever system consisting of a tapered wire with 5 helical loops of decreasing diameter. The catheter is guided into the occluded vessel and passed through the arterial thrombus. The outer catheter is retracted back through the thrombus, leaving the proximal loops of the retrieval system to be deployed and torqued within the thrombus. The ensnared thrombus is then removed.

In this phase I study, the investigators enrolled 30 adult patients in 7 U.S. centers to evaluate the safety and technical efficacy of embolectomy of the cerebral arteries. A total of 28 patients were treated. Inclusion criteria were 1) an acute stroke with National Institutes of Health Stroke Scale score of 10 or higher, 2) presentation between 3 and 8 hours of symptom without contraindications to intravenous thrombolysis, 3) presentation within 3 hours of symptom onset with contraindications to intravenous thrombolysis, 4) angiographic evidence of occlusion of a major cerebral artery, and 5) no large hypodensity on computed tomography. Recanalization of the occluded artery occurred in 12 of 28 (43%) patients. The procedure was well tolerated, and patients with recanalized arteries had better 30-day outcomes (9 of 18) than those whose arteries did not recanalize (0 of 10).

The U.S. Food and Drug Administration approved the Concentric Merci Retrieval System (Concentric Medical, Inc., Mountain View, California) in August 2004 (1). Although this embolus retrieval system requires significant technical expertise and questions remain about how it compares with intra-arterial thrombolysis, it is now available in many hospitals. One key advantage to the technique is its ability to expand the time window for treat-

ment of acute ischemic stroke from 3 to 8 hours. It can also be offered to patients in whom intravenous thrombolysis fails or who are ineligible for intravenous thrombolysis, including those receiving anticoagulation, those who have had recent surgery, and those with left ventricular assist devices.

Addition of Aspirin to Clopidogrel Therapy Increased Risk without Benefit in High-Risk Patients

Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-7. [PMID: 15276392]

After a transient ischemic attack or an ischemic stroke, preventing a second vascular event is critical. Evidence of the benefits of aspirin for secondary prevention is abundant and unambiguous: Aspirin reduces the risk for stroke, myocardial infarction, or death by about 15%. In noncardioembolic ischemic stroke or transient ischemic attack, both clopidogrel therapy and combination therapy with extended-release dipyridamole and aspirin are marginally superior to aspirin therapy alone but cost more than U.S. \$4.20 per day compared with pennies per day for aspirin (2). Warfarin therapy is generally not indicated for secondary stroke prevention except for patients with transient ischemic attack or stroke in the setting of persistent or paroxysmal atrial fibrillation and for some patients with a documented hypercoagulable state, left ventricular ejection fraction of 0.3 or less, carotid or vertebral artery dissection, or patent foramen ovale with an atrial septal defect. For patients already receiving aspirin therapy who have a first transient ischemic attack or stroke, an acceptable strategy is to change to an alternate antiplatelet agent. There is little evidence that adding aspirin provides additional benefit.

Investigators in this study aimed to evaluate the effects of therapy with clopidogrel, alone and in combination with aspirin, for the secondary prevention of vascular events. The study included 7599 high-risk patients who had recent ischemic stroke or transient ischemic attack and at least 1 additional risk factor and who were taking 75 mg of clopidogrel daily. The participants were randomly assigned to receive placebo or additional treatment with aspirin (75 mg/d). Follow-up was 18 months. The combination therapy conferred no significant benefit over clopidogrel for reducing the composite outcome of ischemic stroke, myocardial infarction, vascular death, or rehospitalization secondary to ischemic events (15.7% vs. 16.7%); relative risk

decreased by 6.4% (95% CI, -4.6% to 16.3%) and absolute risk decreased by 1% (CI, -0.6% to 2.7%). However, the risk for life-threatening hemorrhage was significantly increased in the group receiving combination therapy compared with the group receiving clopidogrel therapy alone (96 [2.6%] vs. 49 [1.3%]; absolute risk increase, 1.3 percentage points [CI, 0.6 to 1.9 percentage points]).

In conclusion, combination therapy with clopidogrel and aspirin provided no benefit over clopidogrel alone in the secondary prevention of vascular events in patients with a recent ischemic stroke or transient ischemic attack (and 1 additional vascular risk factor) and increased the risk for serious bleeding. As a result, dual antiplatelet regimens with clopidogrel and aspirin can no longer be recommended as an option for secondary preventive therapy in this patient population.

Simvastatin Therapy Reduced the Incidence of Stroke in High-Risk Patients

Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757-67. [PMID: 15016485]

In addition to antiplatelet therapy, secondary prevention of vascular events in patients with an ischemic stroke or transient ischemic attack should include blood pressure and lipid management and smoking cessation counseling. The investigators of this study randomly assigned 20 536 men (65 years of age or older) with a history of cerebrovascular disease, other occlusive arterial disease, diabetes mellitus, or hypertension with other vascular risk factors to receive simvastatin therapy (40 mg/d) or placebo. During 5 years of treatment, serum low-density lipoprotein cholesterol levels were a mean of 1.05 mmol/L (39 mg/dL) lower in the simvastatin group than in the placebo group. The absolute risk for a primary vascular event (defined as a coronary event, stroke, or a revascularization procedure) was reduced by about 5 percentage points in the simvastatin group (20% risk in the simvastatin group vs. 25% in the placebo group). Benefits were also observed in the subgroup of patients with history of stroke, but the risk reduction was seen in coronary events and revascularization procedures and not in recurrent stroke.

In summary, this study provides evidence to support an expanding role for statin agents in patients with a history of transient ischemic attack or stroke. The magnitude of benefit of simvastatin may be equal to or greater than that provided by antiplatelet therapy. The findings emphasize the need to think of vascular disease broadly: Patients with a history of stroke should be given statin therapy to reduce cardiac vascular events. Statin therapy should be considered in all patients with transient ischemic attacks or stroke with target lowering of serum low-density lipoprotein cholesterol levels to less than 2.60 mmol/L (<100

mg/dL) and possibly less than 1.81 mmol/L (<70 mg/dL) for very-high-risk patients with multiple risk factors. Questions about the role of simvastatin remain, however, for low-risk patients, women, and those with a life expectancy of less than 5 years.

Carotid Artery Stenosis

Carotid Endarterectomy Reduced Stroke Risk in Patients without Neurologic Symptoms

Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised, controlled trial. *Lancet*. 2004;363:1491-502. [PMID: 15135594]

This trial validated and extended the results of the Asymptomatic Carotid Artery Surgery trial published in 1995 (3). This study investigated the benefits of immediate versus delayed carotid endarterectomy in 3120 asymptomatic men with substantial carotid narrowing (diameter reduced by 70% or more as measured by ultrasonography). Immediate carotid endarterectomy reduced the risk for any stroke and perioperative death from 11.8% to 6.4% over the 5-year study period ($P < 0.001$). Beneficial effects, although less prominent, were also seen among women and for fatal or disabling strokes but were not seen in patients who were 75 years of age or older (many of whom died within 5 years of unrelated causes). These results only apply when surgical risk is low. The study did not address how best to screen patients for carotid stenosis.

Benefits of Endarterectomy Were Greatest When Surgery Was Performed within 2 Weeks of an Ischemic Event

Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915-24. [PMID: 15043958]

For this study, the authors analyzed pooled data from the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial to examine factors that might influence the beneficial effects of carotid endarterectomy in symptomatic patients (4, 5). The authors concluded from their analysis of data from 5893 participants that endarterectomy should not be withheld on the basis of age alone if the patient is otherwise deemed medically fit to undergo surgery. In fact, benefit was greatest for those older than age 75 years. To prevent 1 stroke within 5 years, the number needed to treat to prevent 1 ipsilateral stroke was 5 for patients older than 75 years of age versus 18 for patients younger than 65 years of age ($P = 0.030$). The authors also reported that the benefit was greater if the procedure was performed within 2 weeks. The number needed to treat to prevent 1 ipsilateral stroke was

5 for patients who underwent endarterectomy within 2 weeks of the event versus 125 for those who delayed the procedure for more than 12 weeks ($P = 0.009$). Although the degree of stenosis is an important factor to consider when deciding if a symptomatic patient is a good candidate for carotid endarterectomy, this study emphasizes the importance of other factors, including timeliness. If possible, endarterectomy should be performed within 2 weeks of the patient's last symptoms.

Carotid Artery Stenting Was Not Inferior to Carotid Endarterectomy in High-Risk Patients with Carotid Artery Stenosis

Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493-501. [PMID: 15470212]

This study compared carotid stenting with carotid endarterectomy in high-risk patients with carotid artery stenosis (both asymptomatic and symptomatic patients). The U.S. Food and Drug Administration approved the RX ACCULINK Carotid Stent System (Guidant Corp., Santa Clara, California) in late 2004 (6). According to the manufacturer, formal indications for patients with neurologic symptoms include high risk for adverse events from carotid endarterectomy and ultrasonographic or angiographic evidence of at least 50% stenosis of the common or internal carotid artery; the system is also indicated for patients without neurologic symptoms who have stenosis greater than 80% (7). The primary end point of the study was the cumulative incidence at 1 year of death, stroke, myocardial infarction within 30 days, or ipsilateral stroke between 31 days and 1 year. The investigators found that patients in the stenting group had a significantly lower risk for reaching the composite primary end point (cumulative incidence, 12.0% in the stenting group vs. 20.1% in the carotid endarterectomy group; $P = 0.048$). Despite these findings, questions remain about the durability of the procedure and the defined risks and benefits for symptomatic versus asymptomatic patients, patients without comorbid conditions, and women. Although it is reasonable to consider carotid artery stenting rather than carotid endarterectomy when medical conditions greatly increase the risks of surgery or when the stenosis is difficult to assess surgically, restraint is recommended, particularly in those without neurologic symptoms.

Parkinson Disease

L-Dopa Does Not Accelerate Progression of Symptoms in Early Parkinson Disease

Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351:2498-508. [PMID: 15590952]

L-Dopa has been the mainstay of therapy for Parkinson disease for more than 30 years. The drug is taken up by neurons within the substantia nigra where it is converted to dopamine and released from the axon terminals to stimulate the postsynaptic dopamine receptors in the basal ganglia. This dopaminergic stimulation reverses many of the symptoms of Parkinson disease, particularly bradykinesia and rigidity.

Although L-dopa is clinically effective for treating Parkinson disease, particularly in the early stages, *in vitro* research has shown that it has a potential neurotoxic effect. These findings raise the possibility that L-dopa may, if neurotoxic and *in vivo*, hasten the progression of disease.

In this randomized, double-blind trial, 361 patients with early-stage Parkinson disease received L-dopa (150 mg/d, 300 mg/d, or 600 mg/d) or placebo for 40 weeks followed by a 2-week withdrawal period. If L-dopa was neurotoxic and accelerated disease progression, one would expect to see greater deterioration in the L-dopa group than in the placebo group after drug withdrawal. The primary outcome of the study was a change in severity of Parkinson symptoms as measured by scores on the Unified Parkinson Disease Rating Scale between baseline and 42 weeks.

The researchers found that L-dopa was associated with less worsening of parkinsonism than was placebo. Even after withdrawal of L-dopa, these patients had fewer symptoms than those receiving placebo, consistent with the notion that the drug slows disease progression (change in the Unified Parkinson Disease Rating Scale was 7.9 points in the placebo group, 1.9 points in the 150-mg group, 1.9 points in the 300-mg group, and -1.4 points in the 600-mg group; $P < 0.001$).

These data suggest that L-dopa is not neurotoxic and may even be neuroprotective. The authors concluded that physicians and patients can be reassured that L-dopa does not hasten the progression of Parkinson disease. Clinicians should not avoid prescribing L-dopa because of concerns about potential neurotoxicity.

Pergolide May Increase Cardiac Risks

Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet*. 2004;363:1179-83. [PMID: 15081648]

In addition to L-dopa, dopamine agonists are commonly prescribed for patients with Parkinson disease. Dopamine agonists, which include pramipexole, ropinirole, bromocriptine, and pergolide, directly stimulate dopamine receptors within the basal ganglia. Previous studies have associated pergolide with pericardial, retroperitoneal, and pleural fibrosis and with restrictive valvular heart disease; however, these adverse effects, believed to be mediated through serotonin receptors, are thought to be rare.

This case-control study investigated the frequency, severity, dose dependency, and reversibility of restrictive val-

ular heart disease in patients with Parkinson disease who were receiving pergolide therapy. The study included 78 patients who had Parkinson disease treated with pergolide and 18 patients who were never treated with an ergot-derived dopamine agonist (controls). The researchers used a valvular scoring system with a scale ranging from 1 (proven ergot-like restrictive valvular heart disease) to 4 (no disease). The scoring system indicated that 26 of 78 (33%) patients who were exposed to pergolide also had some degree of echocardiographic valvular abnormalities; 15 of 78 (19%) patients had significant valvular disease, and 1 patient required valvular surgery. There were no valvular abnormalities in the 18 controls.

This study was small, and its findings should be confirmed in a larger study, but these data suggest that drug-induced restrictive valvular heart disease may be more common in patients receiving pergolide therapy than previously suspected. Given the availability of other agents to treat Parkinson disease, including non-ergot-derived dopamine agonists (for example, pramipexole and ropinirole), physicians are advised to limit the use of pergolide in affected patients. If pergolide is used at all, patients need to be informed of the potential cardiac risks associated with the drug.

Dementia

Donepezil Therapy Was Efficacious for Mild to Moderate Neuropsychiatric Symptoms of Alzheimer Disease

Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004;63:214-9. [PMID: 15277611]

This study examined the effect of donepezil on neuropsychiatric symptoms, including agitation, anxiety, apathy, and delusions. A total of 134 patients with mild to moderate Alzheimer disease and marked neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI] score of more than 11 points on a 120-point scale) received treatment with donepezil, 5 mg/d, for 6 weeks followed by 10 mg/d for 6 weeks. The investigators then randomly assigned the patients to either continue treatment with donepezil, 10 mg/d, or to receive a placebo. All patients were assessed at 6 weeks and, if there was no marked cognitive deterioration, treatment or placebo was continued for an additional 6 weeks. Symptoms were assessed at the end of each 6-week interval. The 50-point NPI-Distress scale was used to evaluate caregiver stress.

Compared with scores at baseline, NPI scores declined after 12 weeks of donepezil therapy (mean NPI score, 22 vs. 13 points; $P < 0.001$), and all domains of the NPI (except elation) were significantly improved. Caregiver NPI-Distress scores were also improved over baseline (7.9

vs. 13.5 points; $P < 0.001$). After randomization, patients who received donepezil therapy for 12 weeks had improved NPI scores compared with the placebo group (mean change, -2.9 vs. 3.3 points; $P = 0.020$); caregiver NPI-Distress scores were also improved (median change, -2.0 vs. 1.0 points; $P = 0.010$).

This study provides the best evidence to date that donepezil has beneficial effects in patients with mild to moderate Alzheimer disease and moderate behavioral and psychological symptoms of dementia.

More Research Is Needed To Define Appropriate Use of Treatments for Mixed Dementia That Offer Modest Benefits

Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. *JAMA*. 2004;292:2901-8. [PMID: 15598922]

This systematic review evaluated the available studies of treatments for mixed dementia, which is defined as the presence of both Alzheimer dementia and vascular dementia. Research trials have shown statistically significant improvements in cognitive test scores after treatment with cholinesterase inhibitors and the *N*-methyl-D-aspartate antagonist memantine; however, clinical evidence shows that these drugs offer only modest benefits to a small percentage of patients. The authors emphasized that physicians should pursue strategies to improve patients' overall cardiovascular health (such as lifestyle changes and, in some cases, statin therapy) to delay cognitive decline. The potential for benefit should also be weighed against the high cost associated with therapy (combination therapy with a cholinesterase inhibitor and memantine costs approximately \$300 per month). Social workers and community-based services can help patients and families cope with the financial burden of therapy, and they also provide resources to guide decision making related to driving safety, fall risk, and advance directives. The authors suggested that future studies include patients with causes of dementia other than pure Alzheimer and vascular dementia. Further investigation into family attitudes will also help physicians to use medications to meet realistic treatment goals and caregiver expectations.

Dizziness

Methylprednisolone Was More Effective Than Valacyclovir for Recovery of Peripheral Vestibular Function in Patients with Vestibular Neuritis

Strupp M, Zingler VC, Arbusow V, et al. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. *N Engl J Med*. 2004;351:354-61. [PMID: 15269315]

Because vestibular neuritis is thought to be caused by reactivation of herpes simplex virus type 1 infection, many

providers use corticosteroids, antiviral agents, or a combination to treat patients. The efficacy of these agents, however, is unproven.

In this study, the authors randomly assigned 141 patients with acute vestibular neuritis to receive placebo ($n = 38$) or treatment with methylprednisolone ($n = 35$), valacyclovir ($n = 33$), or methylprednisolone plus valacyclovir ($n = 35$). To determine the efficacy of treatment, the investigators measured unilateral vestibular loss by using the peak slow-phase velocity of nystagmus that was induced by caloric irrigation. They assessed vestibular function on the first or second day of hospitalization and at 12 months.

The groups had equivalent severity of vestibular paresis at baseline. The mean improvement in peripheral vestibular function at 12 months of follow-up was 39.6 percentage points (SD, 28.1) in the placebo group, 62.4 percentage points (SD, 16.9) in the methylprednisolone group, 36.0 percentage points (SD, 26.7) in the valacyclovir group, and 59.2 percentage points (SD, 24.1) in the methylprednisolone plus valacyclovir group. A variance analysis showed that methylprednisolone had a significant effect ($P < 0.001$) but valacyclovir did not ($P = 0.43$). Combination therapy was not superior to corticosteroid monotherapy.

In conclusion, these findings demonstrate that a short course of corticosteroid therapy induces a more rapid and complete recovery of peripheral vestibular function in patients with vestibular neuritis than placebo; valacyclovir does not provide a similar benefit.

Self-Treatment with a Modified Epley Procedure Resolved Positional Vertigo

Radtke A, von Brevern M, Tiel-Wilck K, et al. Self-treatment of benign paroxysmal positional vertigo: Semont maneuver vs. Epley procedure. *Neurology*. 2004;63:150-2. [PMID: 15249626]

Benign paroxysmal positional vertigo is a syndrome of brief episodes of severe vertigo that affects older individuals. The vertigo occurs several seconds after change in body position, such as turning in bed or arising from a supine position, and is extinguishable. Calcium carbonate crystals are believed to cause the condition when they dislodge and move within the posterior semicircular canal of the inner ear whenever head position is changed. The flow of endolymph that results activates hair-cell receptors, which causes short-lasting vertigo and mixed torsional and upbeating nystagmus.

The Epley procedure or Semont maneuver can be used to help reposition the crystals within the canal. In the Epley procedure, patients are asked to quickly lie down with their head on a pillow and then turn to the direction of the affected ear, wait 30 seconds, turn their head to the other direction and wait another 30 seconds, then turn their whole body and rise to a sitting position. The theory is that this procedure forces the calcium crystals out of the poste-

rior canal. The Semont maneuver involves having patients turn their head and quickly lean down in the direction of the affected ear, wait 30 seconds, then move quickly in the other direction. In controlled trials, single applications of the Epley procedure or the Semont maneuver relieved symptoms in 70% to 90% of patients; however, some patients required repeated treatment until positional vertigo completely resolved. Complementary self-treatment might be a desirable alternative to medical therapy for benign paroxysmal positional vertigo.

In this trial, the authors examined the efficacy of patients applying the maneuvers themselves at home. The trial compared self-treatment with the Semont maneuver and Epley procedure in 70 patients who had posterior canal benign paroxysmal positional vertigo. Both procedures were modified for self-treatment. The response rate after 1 week, defined as absence of positional vertigo and torsional or upbeating nystagmus, was 95% in the Epley procedure group ($n = 37$) and 58% in the Semont maneuver group ($n = 33$) ($P < 0.001$). Treatment failure was related to incorrect performance of the maneuver in the Semont maneuver group. The modified Epley procedure was simpler to learn and perform. Treatment-related adverse effects did not differ significantly between the groups.

In summary, success rates for self-application of the modified Epley procedure and Semont maneuver ranged from 70% after single application to nearly 100% after repeated application. Because proficiency of technique was less critical for the modified Epley procedure, the authors recommended this strategy as the first-line approach for patients with benign paroxysmal positional vertigo at home.

Epilepsy

Position Statements Provided Helpful Guidance regarding Efficacy and Tolerability of New Antiepileptic Drugs

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1252-60. [PMID: 15111659]

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1261-73. [PMID: 15111660]

These 2 position statements from the American Academy of Neurology provide an excellent review of antiseizure drugs. Carbamazepine, phenytoin, and valproate are still

considered first-line agents for treating seizures. Oxcarbazepine, lamotrigine, and topiramate are the most effective of the newer drugs; all 3 are effective for treating partial seizures, and lamotrigine and topiramate may also be effective for treating primary generalized seizures. According to the position statement, the newer drugs are no better than the older ones for treating seizures; however, they have fewer adverse effects, which will probably improve patient adherence.

Migraine Headaches

Topiramate Prevented Migraine Headaches, but Adverse Effects Were Common

MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. *JAMA*. 2004;291:965-73. [PMID: 14982912]

This multicenter trial examined the efficacy and safety of the antiepileptic drug topiramate for preventing migraine headaches. The study included 483 patients between 12 and 65 years of age who experienced 3 to 12 migraine headaches per month; patients were excluded if they had more than 15 days per 28-day month in which they had a migraine or nonmigraine headache for 30 minutes or more. After a 14-day washout period during which all migraine medications were tapered, patients who met entry criteria were randomly assigned to receive topiramate therapy (50 mg/d, 100 mg/d, or 200 mg/d) or placebo. Topiramate dosages were titrated upward by 25 mg/wk for 8 weeks to the assigned or maximum tolerated dosage, whichever was less. Patients continued to receive that dosage for 18 weeks.

Of 483 patients enrolled in the study, 468 completed at least 1 postbaseline efficacy assessment and made up the intention-to-treat population. Mean monthly migraine fre-

quency decreased significantly in patients receiving topiramate at dosages of 100 mg/d (difference, -2.1 ; $P = 0.008$) and 200 mg/d (difference, -2.4 ; $P < 0.001$). Approximately 25% of the patients in the topiramate groups discontinued therapy because of adverse events that included paresthesias, fatigue, and nausea. Patients treated with topiramate also lost weight, which may make the drug an attractive alternative to other common migraine treatments that often produce weight gain.

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