Cochrane for Clinicians

Putting Evidence into Practice

Antiepileptic Drug Monotherapy for Epilepsy

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Clinical Question

Which is the best antiepileptic drug monotherapy for adults and children with epilepsy?

Evidence-Based Answer

In patients with partial-onset (focal) seizures, levetiracetam (Keppra), lamotrigine (Lamictal), and carbamazepine (Tegretol) were associated with the longest time to treatment withdrawal (i.e., the recommended patient-oriented outcome measure that balances tolerability with effectiveness). In patients with generalized seizure disorder, valproic acid (Depakene) was associated with the longest time to treatment withdrawal.[1] (Strength of Recommendation: A, based on consistent patient-oriented evidence.)

Practice Pointers

Approximately 1.2% of the U.S. population has active epilepsy, including 3 million adults and 470,000 children.[2] Up to 70% of patients with epilepsy will attain remission with appropriate treatment, the majority with antiepileptic drug monotherapy.[3,4] This analysis compared the effectiveness of 10 monotherapy antiepileptic drugs: carbamazepine, gabapentin (Neurontin), lamotrigine, levetiracetam, oxcarbazepine (Trileptal), phenobarbital, phenytoin (Dilantin), valproic acid, topiramate (Topamax), and zonisamide (Zonegran).

This Cochrane review included 36 randomized controlled trials with 12,391 patients. Patients of all ages were pooled for analyses; approximately 67% had partial-onset seizures, 25% had generalized-onset seizures, and 9% had unclassified seizures.[1] The primary outcome was time to withdrawal of allocated treatment, with longer time to withdrawal indicating more successful therapy. Secondary outcomes were six- and 12-month remission of seizures, time to first seizure postrandomization, and treatment-related adverse effects. Outcomes were presented as Cox proportional hazard ratios (HRs), with HRs less than 1.0 being better and HRs greater than 1.0 being worse when compared with control drugs.[1]

In patients being treated for partial seizures, lamotrigine (HR = 0.75; 95% confidence interval [CI], 0.65 to 0.86) and levetiracetam (HR = 0.82; 95% CI, 0.69 to 0.97) had longer times to withdrawal than carbamazepine. Lamotrigine outperformed gabapentin (HR = 1.6; 95% CI, 1.31 to 1.96) and phenobarbital (HR = 2.08; 95% CI, 1.53 to 2.83). Although generally less tolerable, the older antiepileptic drugs including phenobarbital (HR = 0.61; 95% CI, 0.49 to 0.77), phenytoin (HR = 0.76; 95% CI, 0.64 to 0.91), and carbamazepine (HR = 0.78; 95% CI, 0.70 to 0.86) delayed the time to first seizure compared with lamotrigine.

In patients being treated for generalized seizures, valproic acid was superior to carbamazepine (HR = 1.42; 95% CI, 1.09 to 1.85), topiramate (HR = 1.76; 95% CI, 1.22 to 2.53), and phenobarbital (HR = 2.09; 95% CI, 1.17 to 3.75) in time to treatment withdrawal. There were no significant differences between agents in time to six- or 12-month remission for either partial or generalized seizures. Adverse effects associated with antiepileptic drugs included fatigue, headache, gastrointestinal disturbances, dizziness, and skin reactions. Adverse effects were described in narrative format because of variability among studies.

Current National Institute for Health and Care Excellence guidelines recommend carbamazepine or lamotrigine for patients diagnosed with partial seizures, with levetiracetam as a favorable alternative. For generalized seizures, valproic acid is recommended as first-line therapy, with lamotrigine and levetiracetam as alternative options and first-line therapy for women who are or could become pregnant.[5]

The practice recommendations in this activity are available at http://www.cochrane.org/CD011412.

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CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 565.

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Effectiveness and Safety of Celecoxib for the Treatment of Rheumatoid Arthritis

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Clinical Question

Is celecoxib (Celebrex) effective and safe for patients with rheumatoid arthritis (RA)?

Evidence-Based Answer

Compared with placebo, celecoxib improves pain (number needed to treat [NNT] = 4) and clinical symptoms (NNT = 7), but it has no effect on physical function in patients with RA.[1] (Strength of Recommendation [SOR] = A, based on moderate-quality evidence.) Compared with traditional nonsteroidal anti-inflammatory drugs (NSAIDs), celecoxib is no better at improving pain or physical function in patients with RA. Celecoxib causes fewer gastroduodenal ulcers (at least 3 mm in size) than traditional NSAIDs (number needed to harm [NNH] with traditional NSAIDs as opposed to celecoxib = 9).[1] (SOR = A, based on moderate-quality evidence.)

Practice Pointers

RA is a common type of inflammatory arthritis. Although disease-modifying antirheumatic drugs (DMARDs) are first-line therapy to minimize pain and swelling, NSAIDs are commonly used for arthritis analgesia. The authors of this review sought to assess whether celecoxib is an effective and safe agent for treating symptoms of RA.[1]

This review included eight double-blind, randomized, parallel-group trials with 3,988 participants who had been diagnosed with RA for an average of nine years.[1] Most patients (73%) were women. Participants in the intervention arms received celecoxib in a dosage of 200 or 400 mg per day. Outcomes were based on American College of Rheumatology 20% improvement criteria (ACR20), as well as self-reported pain and physical function.

Compared with placebo, celecoxib improved clinical symptoms (15% improvement on ACR20; 95% confidence interval [CI], 7% to 25%; NNT = 7 [95% CI, 5 to 13]). Celecoxib also improved self-reported pain (i.e., 11-point reduction on a 100-point visual analog scale over 12 weeks; 95% CI, 8 to 14; NNT = 4 [95% CI, 3 to 6]). Despite these findings, celecoxib did not improve joint function as defined by the Health Assessment Questionnaire Disability Index scale, which assesses activities of daily living in patients with RA. Although the reviewers looked for reports of cardiovascular events, none were noted in the celecoxib vs. placebo comparison. Short-term serious adverse events, such as headache, dyspepsia, diarrhea, and abdominal pain, and total withdrawals or discontinuation rates were evaluated; there was no difference in the rates of short-term serious adverse events between celecoxib and placebo.

Celecoxib and traditional NSAIDs were equally effective at reducing pain and improving clinical symptoms. Moderate-quality evidence showed that celecoxib caused fewer gastroduodenal ulcers (at least 3 mm in size) than traditional NSAIDs (absolute change = 12%; 95% CI, 11% to 13%; NNH = 9 [95% CI, 8 to 10]). No differences were noted in the number of short-term serious adverse events between patients treated with celecoxib and traditional NSAIDs. There were also no differences in cardiovascular events between patients treated with celecoxib and those treated with traditional NSAIDs. Finally, fewer patients discontinued celecoxib therapy (7%) than traditional NSAID therapy (14%; absolute change = 7%; 95% CI, 4% to 9%; NNH = 14 [95% CI, 11 to 23]).

Of note, five out of eight studies in the review were funded by pharmaceutical companies; seven studies were rated as being at high or unclear risk of attrition bias.

There is currently no cure for RA. Although U.S. and Canadian guidelines support the use of DMARDs, they do not discuss the role of NSAIDs for RA. This review suggests there may be a role for the use of celecoxib in the care of RA.[2]

The practice recommendations in this activity are available at http://www.cochrane.org/CD012095.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the U.S. government.

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