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When to Discontinue Antiepileptic Drug Therapy for Patients in Remission

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Clinical Question

In patients with a history of epilepsy, how long must one be seizure-free before stopping antiepileptic drug therapy?

Evidence-Based Answer

Children with epilepsy should be seizure-free for at least two years before stopping antiepileptic drug therapy, especially those who have partial seizures or a history of abnormal electroencephalography (EEG) results. Evidence is insufficient to guide this decision for children with generalized seizures, and there is no evidence with which to answer this question for adults. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Patients sometimes present to their family physician requesting discontinuation of their seizure medication, yet doing so prematurely can be harmful. A detailed history is important to establish whether seizures were focal (partial) or generalized (involving bilateral hemispheres of the brain), and whether consciousness was impaired. Attempts should be made to retrieve EEG or imaging study results. Furthermore, some patients may have had nonepileptic (psychogenic) seizures or seizures provoked by a resolved stimulus (e.g., fever, alcohol or drug withdrawal).[1]

The authors of this Cochrane review assessed the risk of discontinuing antiepileptic drug therapy in children and adults with true epilepsy. They defined epilepsy as two or more unprovoked seizures at least 24 hours apart, one seizure with very high risk of recurrence because of an underlying condition, or a diagnosis of epilepsy syndrome. The authors searched for randomized controlled trials comparing patients with epilepsy who underwent early (less than two continuous years seizure-free) vs. late (two or more years seizure-free) withdrawal of antiepileptic drugs. Neonates were excluded. Five trials with a total of 924 children were ultimately included in the meta-analysis; the most recent trial was published in 2000.

Four of the trials were conducted in affluent European countries, and one took place in Ethiopia. Blinding of groups was not considered feasible or ethical. The studies lasted from six months to seven years and included an initial taper of antiepileptic drugs over one month to one year. Overall, late withdrawal of antiepileptic drugs decreased the risk of seizure relapse (34% vs. 46%; $P < .001$; number needed to treat = 8) compared with early withdrawal.

The studies included heterogeneous patient populations with different seizure types who were receiving different medications and undergoing various taper protocols. Abnormal EEG findings increased the risk of relapse (pooled relative risk = 1.44; 95% confidence interval, 1.13 to 1.83; $P = .003$). Other factors that increased the risk of seizures included diagnosis of seizure disorder before two years or after 10 years of age, history of status epilepticus, an intellectual disability (IQ lower than 70), and a high seizure frequency before and during treatment. Only one trial included patients with generalized seizures; no conclusion could be reached regarding risk of relapse.

In 1994, the American Academy of Neurology published guidelines recommending discontinuation of antiepileptic drug therapy if the following criteria are met: seizure-free for two to five years, only one type of epilepsy, normal EEG findings, and normal neurologic examination findings.[2] The Italian League Against Epilepsy recommends a minimum of two years seizure-free and tapering of antiepileptic drugs over at

least six months.[3] A 2010 review of randomized and nonrandomized trials addressed risk factors affecting the prognosis after discontinuing medication.[4] The author concluded that sudden death and development of a treatment-refractory, resistant form of epilepsy are rare and should not be emphasized in the shared decision-making process.

SOURCE: Strozzi I, Nolan SJ, Sperling MR, Wingerchuk DM, Sirven J. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev.* 2015;(2):CD001902.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD001902.

REFERENCES

1. Wilden JA, Cohen-Gadol AA. Evaluation of first nonfebrile seizures. *Am Fam Physician.* 2012;86(4):334-340.
2. American Academy of Neurology Quality Standards Subcommittee. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients—summary statement. *Neurology.* 1996;47(2):600-602.
3. Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: guidelines of the Italian League Against Epilepsy. *Epilepsia.* 2013;54(suppl 7):2-12.
4. Hixson JD. Stopping antiepileptic drugs: when and why? *Curr Treat Options Neurol.* 2010;12(5):434-442.

Topical Antihistamines and Mast Cell Stabilizers for Treating Allergic Conjunctivitis

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Clinical Question

Are topical antihistamines and mast cell stabilizers, used alone or in combination, effective and safe in treating patients with seasonal and perennial allergic conjunctivitis?

Evidence-Based Answer

Topical antihistamines and mast cell stabilizers, either alone or in combination, are safe and effective for reducing the symptoms of seasonal and perennial allergic conjunctivitis. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.) There is insufficient evidence to compare the effectiveness of specific topical medications. No serious adverse effects are associated with these medications.

Practice Pointers

Patients with seasonal allergic conjunctivitis and perennial allergic conjunctivitis often report itching, tearing, swollen eyelids, and redness mediated by the release of histamine from mast cells, resulting in conjunctival inflammation.[1,2] Itching is the most common symptom, occurring in more than 75% of patients. The authors of this Cochrane review evaluated the effectiveness of topical mast cell stabilizers and antihistamines for this common condition.

This review included 30 randomized controlled trials with 4,344 participants four to 85 years of age who had seasonal or perennial allergic conjunctivitis. Studies of patients with vernal keratoconjunctivitis, atopic keratoconjunctivitis, or giant papillary conjunctivitis were excluded, as were studies that analyzed oral or nasal antihistamines. Within the 30 trials, 17 different drug or treatment comparisons were conducted in North and South America, Asia, Europe, Africa, and Australia; the duration of the studies ranged from one to eight weeks. The primary outcomes were participant reports of photophobia and ocular itching, irritation, and watering. Secondary outcomes included adverse effects; the duration of acute symptoms; the incidence of acute episodes per year; and signs of hyperemia, chemosis, or tarsal papillae on examination. The risk of bias was judged to be low.

Overall, the results favor topical antihistamines and mast cell stabilizers, alone or in combination, vs. placebo for short-term relief of the symptoms of allergic conjunctivitis *(Table 1)*. Eight studies comparing the mast cell stabilizers nedocromil (Alocril) or cromolyn

Table 1. Topical Treatments for Allergic Conjunctivitis

Drug class	*Dosing schedule*	*Cost**
Antihistamines		
Bepotastine (Bepreve)	Twice per day	NA ($180)
Emedastine (Emadine)	Four times per day	NA ($120)
Epinastine (Elestat)	Twice per day	$38 ($220)
Mast cell stabilizers		
Lodoxamide (Alomide)	Four times per day	NA ($150)
Nedocromil (Alocril)	Twice per day	NA ($190)
Pemirolast (Alamast)	Four times per day	NA ($115)
Combination formulations		
Azelastine†	Up to four times per day	$40
Ketotifen (Zaditor)†	Twice per day	NA ($15)
Olopatadine (Patanol)	Twice per day	$50 ($250)

NA = not available.

**—Estimated retail cost for one month of therapy based on information obtained at http://www.goodrx.com (accessed April 13, 2016). Generic price listed first; brand price listed in parentheses.*
†—Available over the counter without a prescription.

sodium vs. placebo favored the mast cell stabilizers. Trials comparing the antihistamines azelastine (nine studies) and levocabastine (not available in the United States; five studies) vs. placebo all favored the antihistamines. Because of heterogeneity between studies, meta-analysis was possible only for four studies with 204 patients that compared the effect of olopatadine (Patanol) with ketotifen (Zaditor) on itching and tearing at 14 days. In this analysis, olopatadine was superior to ketotifen overall in reducing itching (mean difference = −0.32; 95% confidence interval, −0.59 to −0.06) but equivalent in reducing tearing. The evidence was insufficient to make any other drug comparisons. There were no serious adverse effects related to treatment with topical medications.

Clinical guidelines from the American Academy of Ophthalmology[3] and the College of Optometrists[4] (England) for the management of allergic conjunctivitis support the use of topical antihistamines and topical mast cell stabilizers, either alone or as combined formulations.

SOURCE: Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. *Cochrane Database Syst Rev.* 2015;(6):CD009566.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD009566.

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REFERENCES

1. Williams DC, Edney G, Maiden B, Smith PK. Recognition of allergic conjunctivitis in patients with allergic rhinitis. *World Allergy Organ J.* 2013;6(1):4.
2. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol.* 2005;115(1):118-122.
3. American Academy of Ophthalmology. Conjunctivitis PPP–2013. http://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013. Accessed August 5, 2015.
4. College of Optometrists. Clinical management guidelines: seasonal allergic conjunctivitis (hay fever conjunctivitis); perennial allergic conjunctivitis. http://www.college-optometrists.org/en/utilities/document-summary.cfm/docid/281E5349-E39C-4E81-AEBC3B57F1379BF5. Accessed April 12, 2016. ■