

## Are Neuraminidase Inhibitors Effective for Preventing and Treating Influenza in Healthy Adults and Children?

WILLIAM E. CAYLEY, JR., MD, MDiv, *University of Wisconsin Department of Family Medicine, Eau Claire, Wisconsin*

The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Cayley presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD008965>.



This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 611.

The series coordinator for *AFP* is Kenneth W. Lin, MD, Department of Family Medicine, Georgetown University School of Medicine, Washington, DC.

A collection of Cochrane for Clinicians published in *AFP* is available at <http://www.aafp.org/afp/cochrane>.

### Clinical Scenario

A previously healthy man presents in the middle of the influenza season with a one-day history of cough, myalgias, and a fever of 101°F (38.3°C). He asks if there is a medication to help treat his illness and to prevent his wife and children from becoming sick.

### Clinical Question

Are neuraminidase inhibitors effective for preventing and treating influenza in healthy adults and children?

### Evidence-Based Answer

Treating previously healthy patients with oseltamivir (Tamiflu) reduces the duration of influenza symptoms by approximately 21 hours, but it does not reduce the risk of hospitalization in this population.<sup>1</sup> The data are insufficient to determine whether oseltamivir reduces the complications or transmission of influenza. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

Guidelines from the Centers for Disease Control and Prevention (CDC) recommend early antiviral treatment for influenza to reduce the duration of fever and other symptoms, reduce the risk of complications, and shorten the length of stay for those hospitalized.<sup>2</sup> Currently, the guidelines advise using only the neuraminidase inhibitors oseltamivir and zanamivir (Relenza) because of increasing resistance of influenza viruses to the older adamantanes (amantadine and rimantadine [Flumadine]).<sup>3</sup>

A recent Cochrane review of neuraminidase inhibitors for the prevention and treatment of influenza in children reported that

zanamivir and oseltamivir reduced the risk of developing influenza after exposure to a case in the household (absolute risk reduction = 8 percent), although there was an increased risk of vomiting with oseltamivir compared with placebo. In treatment trials, neuraminidase inhibitors reduced illness duration by 1.3 to 2.8 days, and oseltamivir reduced the incidence of acute otitis media in children one to five years of age. An important limitation to this review is that it considered data only from published trials.<sup>4</sup>

A 2010 Cochrane review of neuraminidase inhibitors for influenza prevention and treatment in healthy adults, which was previously reviewed in "Cochrane for Clinicians,"<sup>5</sup> reported that these medications reduced the risk of contracting symptomatic, confirmed influenza and reduced the time to recovery for those with laboratory-confirmed influenza.<sup>6</sup> However, the authors subsequently identified discrepancies between the results of the published medical literature used in their review and the clinical study reports made available by the manufacturer of oseltamivir. This updated review focuses on the effectiveness of oseltamivir in healthy adults and children as documented in the clinical study reports of published and unpublished trials.<sup>1</sup>

The authors found that, based on clinical study reports, treatment with oseltamivir reduced the likelihood of an antibody response to influenza, the diagnostic marker that is typically used to determine the effectiveness of prophylaxis. In the absence of another way to measure the effectiveness of oseltamivir prophylaxis, it is uncertain whether the medication reduces the risk of influenza transmission.<sup>1</sup>

Based on comprehensive data from five randomized controlled trials of treatment of

## Cochrane Abstract

**Background:** Neuraminidase inhibitors are thought to help reduce the symptoms of influenza, with several possible mechanisms proposed. However, the evidence base for this class of agents remains a source of debate. In a previous review, we documented substantial risks of publication bias in trials of neuraminidase inhibitors for influenza (60 percent of patient data from phase III treatment trials of oseltamivir [Tamiflu] have never been published) and reporting bias in the published trials. Since that time, we have become aware of a large number of unpublished trials of neuraminidase inhibitors in the management of influenza; this review updates and merges existing reviews in this area.

**Objectives:** To review clinical study reports of placebo-controlled randomized trials, regulatory comments, and reviews ("regulatory information") of the effects of the neuraminidase inhibitors, oseltamivir and zanamivir (Relenza), for influenza in all age groups, and to appraise trial programs, rather than single studies. Clinical study reports are very detailed, unpublished clinical trial data containing in-depth descriptions of protocol rationale, methods analysis plans, trial results, and organizational documents (such as contracts).

**Search Methods:** We searched trial registries, cross-referencing published and unpublished sources, and corresponded with manufacturers and regulators. We searched the archives of the U.S. Food and Drug Administration and European and Japanese regulators. The evidence in this review reflects searches to obtain relevant information up to April 12, 2011.

**Selection Criteria:** We included regulatory information based on assessments of randomized controlled trials conducted in persons of any age who had either confirmed or suspected influenza, or who had been exposed to influenza in the local community or their place of residence.

**Data Collection and Analysis:** We indexed regulatory information in two purpose-built instruments and reconstructed trials using CONSORT statement-based templates. To progress to Stage 2 (full analysis), we sought manufacturer explanations of discrepancies in the data. GlaxoSmithKline offered us individual patient data and responded to our queries, but Roche did not provide us with complete clinical study reports. In Stage 2, we intended to analyze trials with validated data (i.e., assuming our validation questions aimed at clarifying omissions and discrepancies were resolved). No studies progressed to Stage 2. We carried out analyses of the effects of oseltamivir on time to first alleviation of symptoms and hospitalizations using the intention-to-treat population, and tested five hypotheses generated after protocol publication.

**Main Results:** We included and analyzed data from 25 studies (15 oseltamivir and 10 zanamivir studies). The studies had adequate randomization and blinding procedures, but imbalances in the available analysis populations (intention-to-treat influenza-infected) left many of the studies at risk of attrition bias. All the studies were sponsored by manufacturers of neuraminidase inhibitors. Time to first alleviation of symptoms in persons with influenza-like illness symptoms (i.e., intention-to-treat population) was a median of 160 hours (range: 125 to 192 hours) in the placebo groups, and oseltamivir shortened this by around 21 hours (95% confidence interval [CI], -29.5 to -12.9 hours;  $P < .001$ ; five studies), but there was no evidence of effect on hospitalizations based on seven studies with a median placebo group event rate of 0.84 percent (range: 0 to 11 percent; odds ratio [OR] = 0.95; 95% CI, 0.57 to 1.61;  $P = .86$ ). These results are based on the comprehensive intention-to-treat population data and are unlikely to be biased. A post-protocol analysis showed that participants randomized to oseltamivir in treatment trials had reduced odds of being diagnosed with influenza (OR = 0.83; 95% CI, 0.73 to 0.94;  $P = .003$ ; eight studies), probably because of an altered antibody response. Zanamivir trials showed no evidence of this.

Due to limitations in the design, conduct, and reporting of the trial program, the data available to us lacked sufficient detail to credibly assess a possible effect of oseltamivir on complications and viral transmission. We postponed analysis of zanamivir evidence because of the offer of individual patient data from its manufacturer. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche), despite making five requests between June 2010 and February 2011. No substantial comments were made by Roche on the protocol of our Cochrane Review, which has been publicly available since December 2010.

**Authors' Conclusions:** We found a high risk of publication and reporting biases in the trial program of oseltamivir. Subpopulation analyses of the influenza-infected population in the oseltamivir trial program are not possible because the two arms are noncomparable due to oseltamivir's apparent interference with antibody production. The evidence supports a direct oseltamivir mechanism of action on symptoms, but we are unable to draw conclusions about its effect on complications or transmission of influenza. We expect full clinical study reports containing the study protocol, reporting analysis plan, statistical analysis plan, and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.



These summaries have been derived from Cochrane reviews published in the Cochrane Database of Systematic Reviews in the Cochrane Library. Their content has, as far as possible, been checked with the authors of the original reviews, but the summaries should not be regarded as an official product of the Cochrane Collaboration; minor editing changes have been made to the text (<http://www.cochrane.org>).

persons with symptomatic influenza, oseltamivir reduced the duration of influenza symptoms by 21 hours compared with placebo, although this conclusion is limited by incomplete data and the failure to account for possible symptom relapse. Based on seven

randomized controlled trials, oseltamivir had no statistically significant effect on incidence of hospitalization for patients with influenza. Significantly, there is no evidence from these clinical study reports that oseltamivir treatment reduced influenza complications,<sup>1</sup> a

## Cochrane for Clinicians

conclusion that differs from previous reviews that included published trials only.<sup>4-6</sup>

An accompanying editorial published with this Cochrane review discusses how the novel methods it used to comprehensively review data from unpublished studies bring up questions of data access, data completeness, and even mechanisms of action that may mislead systematic reviewers who use information only from published studies.<sup>7</sup> The contrast between the limited positive findings of this review and the strong support for treatment with neuraminidase inhibitors in public health guidelines (such as those from the CDC) highlights the importance of ongoing assessment of such recommendations and related educational materials, especially when evidence to support widespread implementation of an expensive intervention is lacking. This Cochrane review raises questions about the usefulness of antiviral treatments for influenza in healthy persons, and sets a new methodological standard for the development of the evidence base for medical practice.

*Address correspondence to William E. Cayley, Jr., MD, MDiv, at bcayley@yahoo.com. Reprints are not available from the author.*

**Author disclosure:** No relevant financial affiliations to disclose.

### REFERENCES

1. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2012;1:CD008965.
2. Centers for Disease Control and Prevention. 2011-2012 Influenza antiviral medications: summary for clinicians. August 2011. <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>. Accessed June 5, 2012.
3. Centers for Disease Control and Prevention. Antiviral drug-resistance among influenza viruses. August 2011. <http://www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm>. Accessed June 5, 2012.
4. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). *Cochrane Database Syst Rev*. 2012;4:CD002744.
5. Cayley WE Jr. Neuraminidase inhibitors for influenza treatment and prevention in healthy adults. *Am Fam Physician*. 2010;82(3):242-244.
6. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev*. 2010;(2):CD001265.
7. Lasserson T, Tovey D. Neuraminidase inhibitors for influenza: methods change, principles don't. *Cochrane Database Syst Rev*. 2012;2:ED000038. ■

# MOVING?

To ensure uninterrupted delivery of *American Family Physician*, be sure to give us at least six weeks' advance notice of your move!

### Send to the APPROPRIATE ADDRESS:

#### PHYSICIANS WHO ARE NOT MEMBERS OF AAFP

Send old and new address to the American Medical Association or the American Osteopathic Association. The AAFP office cannot make these address changes.

AMA Dept. of Census & Self-Reported Data  
515 N State St, Chicago, IL 60610  
Phone: (800) 262-2350 / Fax: (866) 536-0645  
E-mail: [addresschange@ama-assn.org](mailto:addresschange@ama-assn.org)

OR

AOA Records Dept.  
142 E Ontario St, Chicago, IL 60611  
Phone: 312-202-8284  
E-mail: [msc@osteopathic.org](mailto:msc@osteopathic.org)

#### PAID SUBSCRIBERS OF AFP

AAFP Contact Center  
11400 Tomahawk Creek Parkway  
Leawood, KS 66211-2680  
Phone: 800-274-2237 / Fax: 913-906-6075  
E-mail: [contactcenter@aafp.org](mailto:contactcenter@aafp.org)

#### MEMBERS OF AAFP

AAFP Contact Center  
11400 Tomahawk Creek Parkway  
Leawood, KS 66211-2680  
Phone: 800-274-2237 / Fax: 913-906-6075  
E-mail: [contactcenter@aafp.org](mailto:contactcenter@aafp.org)

Both your OLD and NEW addresses are needed. Please send a copy of the journal cover with your old address and legibly print your new address, or use the form below. Include your name and ID number.

#### Print OLD address here:

Name \_\_\_\_\_ ID Number \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip Code \_\_\_\_\_

#### Print NEW address here: work home

Address \_\_\_\_\_

City \_\_\_\_\_ State 9-digit Zip Code \_\_\_\_\_

Phone \_\_\_\_\_ E-mail or Fax \_\_\_\_\_