

---

## Use of the Neuraminidase Inhibitor Class of Antiviral Drugs for Treatment of Healthy Adults With an Acute Influenza-like Illness

This systematic review abstract is taken from Jefferson T, Demicheli V, Deeks J, Rivette D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults (Cochrane review). In: The Cochrane Library. Issue 2. Oxford, United Kingdom: Update Software; 2001.

### EBEM Commentator

Stephen R. Pitts, MD, MPH  
Department of Emergency Medicine  
Emory University School of Medicine  
Atlanta, GA

Reprints not available from the commentator.

**Address for correspondence:** Stephen R. Pitts, MD, MPH, Department of Emergency Medicine, Emory University School of Medicine, 69 Butler Street, Atlanta, GA 30303; E-mail [pitts@sph.emory.edu](mailto:pitts@sph.emory.edu).

Copyright © 2002 by the American College of Emergency Physicians.

0196-0644/2002/\$35.00 + 0

47/1/123590

doi:10.1067/mem.2002.123590

---

## Use of the Neuraminidase Inhibitor Class of Antiviral Drugs for Treatment of Healthy Adults With an Acute Influenza-like Illness

---

[Pitts SR. Use of the neuraminidase inhibitor class of antiviral drugs for treatment of healthy adults with an acute influenza-like illness. *Ann Emerg Med.* May 2002;39:552-554.]

---

### TAKE HOME MESSAGE

There is sufficient evidence to conclude that the neuraminidase inhibitors (oseltamivir and zanamivir) reduce symptom duration slightly when administered early in healthy adults with a high likelihood of influenza. Both drugs infrequently cause gastrointestinal symptoms, especially nausea.

---

### OBJECTIVE

To determine whether the neuraminidase inhibitor class of antiviral drugs improves symptoms in healthy adults with influenza or influenza-like illness.

---

### DATA SOURCES

The Cochrane Acute Respiratory Infections Group searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Registry electronically in May 1999, and hand-searched the journal *Vaccine* through 1997. They also contacted the manufacturers of oseltamivir (Gilead Sciences, Inc., Foster City, CA, partnering with Hoffman-LaRoche Ltd, Basel, Switzerland) and zanamivir (Glaxo SmithKline, Research Triangle Park, NJ) when necessary. This review was last updated in October 18, 2000.

---

## PATIENT SELECTION

A study was included if its participants were apparently healthy individuals, if participants were mainly adults, that is, if more than 75% were between the ages of 14 and 60 years, and if the study included time to improvement of symptoms as an outcome. The quality of individual studies was graded but did not serve as an exclusion criterion.

---

## DATA EXTRACTION

Two authors independently graded each trial and obtained its results. When there was a conflict, a third author arbitrated. The primary outcomes assessed included time to alleviation of symptoms and time to return to normal activities, and adverse effects evaluated in the meta-analysis included nasal irritation and gastrointestinal and upper respiratory side effects. Results were analyzed separately for patients with clinically suspected and laboratory-proven influenza.

---

## MAIN RESULTS

Only 4 studies, 2 each comparing zanamivir and oseltamivir to placebo, were available when this review was last updated (2000). All were randomized trials, but further detail on methods, such as quality of allocation concealment, could not be abstracted from the brief reports available at the time. Control patients (mean arm size 107) had symptoms 5 to 6 days on average. The weighted mean difference (reduction) in symptom duration was 1.0 days (95% confidence interval [CI] 0.6 to 1.3) for patients with clinically suspected influenza and 0.9 days (95% CI 0.2 to 1.6) for patients with laboratory-confirmed influenza. There were a mean of 87 experimental participants per arm in the zanamivir trials and 920 per arm in the oseltamivir trials.

Side effect assessment was performed separately for amantadine and oseltamivir. Compared with placebo, there was an increase in gastrointestinal side effects, defined as dyspepsia or nausea, in the single interpretable zanamivir treatment trial (odds ratio [OR] 2.6; 95% CI 1.6 to 4.2). There was also an increase in nausea in the oseltamivir trial (OR not calculated) that increased with oseltamivir dose. For these reasons, future trials will use 75 mg rather than 150 mg, because they are of equal efficacy.

---

## CONCLUSIONS

The preliminary reports available at the time of the last update of this review have since been complemented by full articles, without changing this review's conclusions (see references at the end of this article). Both zanamivir and oseltamivir reduce symptom duration by 1 day for patients who have had an influenza-like illness for less than 2 days. Nausea or dyspepsia occur slightly more frequently with both drugs than placebo.

### Author Contact

Thomas Jefferson, MD, MRCP, FFPHM

Health Reviews Ltd

Rome, Italy

E-mail [toj1@aol.com](mailto:toj1@aol.com)

---

## COMMENTARY: CLINICAL IMPLICATION

Acute influenza-like illness (ILI), defined by the Centers for Disease Control and Prevention as "temperature of higher than 100°F with cough or sore throat," begins overwhelming emergency departments across the world each autumn and continues to do so until late winter.<sup>1</sup> A small, poorly identifiable subgroup of these patients (up to 35% in especially severe seasons) will have an influenza viral infection during the brief peak of the influenza epidemic. Although amantadine and rimantadine of the influenza A-specific M-protein inhibitor class of antiviral drugs have been available for several years, they are ineffective against influenza B and cause impressive side effects in the elderly.<sup>1</sup> The new neuraminidase inhibitor (NAI) class of antiviral drugs claims to be effective against serotypes A and B and cause less side effects. The 2000 to 2001 season saw a preponderance of influenza B, but serotype B does not circulate every season. The NAI category is currently represented by 2 drugs—oseltamivir, an orally ingested capsule, and zanamivir, an inhaled powder.

Given the high prevalence of respiratory illnesses during the winter months and their potential to further stretch an already strained acute care infrastructure and the self-limited nature of influenza-like illnesses among healthy adults, many emergency physicians might justifiably wish to discourage patients from visiting the ED to obtain these new agents. However, the Jefferson review indicates that the NAIs are indeed effective at reducing

influenza symptoms. Although it was last updated a year ago, which is a long time in this rapidly progressing field, subsequently published papers do not contradict these findings.<sup>2,3</sup> Because the oseltamivir trials included relatively few patients with influenza B, unlike zanamivir, it has not yet been licensed for use in Europe.

There are several reasons to be cautious in interpreting the results of this review. First, most ED patients with ILI will have had symptoms for more than 2 days and thus will not benefit from any antiviral drugs. Second, the cumulative sample sizes in these trials are small enough to be compatible with significantly different estimates of effectiveness. Third, concern that inhaled zanamivir might be ineffective or even worsen symptoms for patients with reactive airways has led the manufacturer to discourage its use in this subgroup. Fourth, the cost of these drugs is not trivial, and many patients without drug benefit coverage will not be able to afford their prescription.

Finally, in the pooled NAI studies, there was only a small difference in effectiveness between those patients clinically suspected of having influenza and those with laboratory-proven infection. This would be very surprising if the “clinically suspected” group were similar to patients with ILI in a clinical practice, few of whom have influenza. However, the prevalence of influenza in these clinical trials was ultimately found to be greater than 50%, suggesting that some patient selection on clinical grounds had occurred to boost the yield of true cases. Performance of NAIs in a realistic practice setting has yet to be evaluated and will likely find the drugs to be somewhat less effective unless new strategies that incorporate validated clinical and rapid bedside tests allow us to target patients who are more likely to benefit.

In conclusion, the reviewers found that the NAI class of antiviral drugs does reduce mean symptom duration in patients strongly suspected of having influenza. Gastrointestinal side effects were infrequent and not severe. This class of drugs would be safer for the elderly and for patients with renal failure or seizures than the previous class of antiviral drugs and may be a useful in the fight against influenza in the ED.

---

#### EVIDENCE-BASED MEDICINE TEACHING POINTS

**Efficacy Analysis.** When the final diagnosis is uncertain at the time of treatment allocation, but can be determined later, as in studies of analgesics for renal colic or antivirals for influenza, a separate analysis of the patients ultimately found to have the relevant disease is often published as

the “efficacy analysis.” More relevant to clinicians is usually the analysis of the unselected patient group, or the “effectiveness analysis.” The efficacy analysis usually shows a greater treatment effect than the latter, although random fluctuation reversed that tendency nonsignificantly in this Cochrane review. In the more recent review of zanamivir trials cited, the efficacy analysis indeed demonstrated a 1.5-day benefit compared with 1 day in the effectiveness analysis.<sup>3</sup>

1. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2000;49(No. RR-3):1-38.

2. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA.* 2000;283:1016-1024.

3. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimicrobial Chemotherapy.* 1999;44(Suppl B):23-29.