

# Are Amantadine and Rimantadine Effective in Healthy Adults With Acute Influenza?

## EBEM Commentator Contact

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the *Cochrane Database of Systematic Reviews* and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Jefferson T, Deeks JJ, Demicheli V, et al. Amantadine and rimantadine for preventing and treating influenza A in adults (Cochrane review). In: *Cochrane Database Syst Rev*. 2004;3:CD001169.

## OBJECTIVE

To assess the effectiveness and safety of amantadine and rimantadine for the prevention and treatment of influenza A in healthy adults.

## DATA SOURCES

The authors report a comprehensive search of the Cochrane Central Register of Controlled Trials, *The Cochrane Library* Issue 4, 2003; MEDLINE from January 1966 to November week 2, 2003; EMBASE from January 1990 to September 2003; and reference lists of articles. The reviewers also contacted manufacturers, researchers, and authors for additional published and unpublished studies. The review is considered updated to February 2005.

## STUDY SELECTION

Randomized and quasirandomized studies comparing amantadine or rimantadine with placebo, control antivirals or no intervention, or comparing doses or schedules of amantadine or rimantadine in healthy adults.

## DATA EXTRACTION AND ANALYSES

Two reviewers independently selected articles for inclusion, evaluated methodologic quality of the studies, and abstracted the data. Continuous variables were reported as weighted mean difference, and dichotomous variables were reported as relative risk (RR) with associated 95% confidence intervals (CIs). A random-effects model was used, based on the study's heterogeneity. For prevention trials, the numbers of participants with clinical influenza (influenza-like illness), confirmed

influenza A, and adverse effects were analyzed. Analysis for treatment trials included the mean duration of fever and length of hospital stay and the number of adverse effects.

## MAIN RESULT

Twenty prevention trials and 11 treatment trials were included in this review; no unpublished studies were identified. Amantadine prevented 25% of influenza-like illness cases (95% CI 13% to 36%), and 61% of influenza A cases (95% CI 35% to 76%). Amantadine reduced the duration of fever by 1 day (95% CI 0.7 to 1.3 days). Rimantadine demonstrated comparable effectiveness, but there were fewer trials, and the results for prevention were not statistically significant. Both amantadine and rimantadine induced significant gastrointestinal adverse effects. Adverse effects of the central nervous system and study withdrawals were significantly more common with amantadine than rimantadine.

## CONCLUSIONS

Amantadine and rimantadine have comparable effectiveness in the prevention and treatment of influenza A in healthy adults; however, the reviewers considered rimantadine superior because it caused fewer adverse effects than amantadine.

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## COMMENTARY: CLINICAL IMPLICATION

Influenza is a common emergency department (ED) presentation during the winter in North America, characterized by fever, coryza, myalgia, fatigue, and cough. Two serotypes (A and B) are recognized, and influenza vaccination is recommended for all health care professionals. Traditional treatment consists of supportive care, rehydration, and the use of antiviral agents in selected populations. Antiviral agents such as rimantadine and amantadine have been used for prevention and treatment in epidemics of serotype A. The newer neuraminidase inhibitor class of antiviral drugs claims to be effective against serotypes A and B and cause fewer adverse effects.<sup>1</sup>

This Cochrane review collected all available evidence for the treatment and prevention of influenza with rimantadine and amantadine. Using high-quality methods and comprehensive searching, this review concludes that rimantadine is preferred over amantadine for the treatment and prevention of influenza A. The efficacy of both drugs for prevention and treatment (within 48 hours of symptom onset) was similar, although the available data are limited, especially for rimantadine. The primary basis for this recommendation lies in the more favorable adverse effect profile of rimantadine. However, the review describes the difficulty in defining the difference in that several studies report data on adverse effects without stratifying for severity. The frequency of reported gastrointestinal adverse effects is roughly equivalent for both drugs; neurologic adverse effects are more frequent with amantadine. When considering neurologic adverse effects, the number needed to harm with amantadine use over rimantadine is 8 (95% CI 4 to 24). In the United States, the current retail cost of a 5-day twice-daily course of rimantadine is approximately \$24 compared with \$3 for amantadine.

Neither amantadine nor rimantadine is effective against influenza B. Given the availability of the neuraminidase inhibitors (eg, oseltamivir, zanamivir) that are effective against both influenza A and B,<sup>1</sup> some discussion of the impact and epidemiology of influenza B is warranted. The incidence of influenza B is highly variable from year to year. For example, during the 2003 to 2004 flu season, there was little influenza B activity across all 9 Centers for Disease Control and Prevention surveillance regions.<sup>2</sup> Although influenza A tends to predominate, wide variability across regions is not uncommon for any given year. In the 2002 to 2003 season, the ratio of A:B isolates was 1:1.4 in the West South Central region (Texas, Oklahoma, Arkansas, Louisiana). The A:B ratio for the same season in the Mid-Atlantic region (New York, Pennsylvania, New Jersey) was 1:0.17. In other words, influenza B was isolated at roughly 1.5 times the rate of A in the Southwest; in the Mid-Atlantic states, influenza A was isolated about 6 times more often than B. Many state and local health departments are developing enhanced flu surveillance with timely reports. Knowledge of local epidemiology, along with selective rapid influenza testing, may help direct clinicians' choice of antiviral agents for influenza.

The specter of avian-based pandemic flu is expected to affect the choice and use of antiviral therapy.<sup>3</sup> The H5N1 strain isolated from humans in Asia has demonstrated resistance to amantadine and susceptibility to oseltamivir,<sup>4</sup> which has led to stockpiling of oseltamivir as part of pandemic flu preparedness.

The Cochrane review also addresses the use of rimantadine and amantadine as preventive therapies after influenza A exposure. Both were found to be clearly and similarly effective in this role. The degree to which prophylactic antiviral therapy is recommended for close contacts of ED patients is not described. In the authors' experience, this is not a common practice in the ED setting. It is probably prudent that the emergency physician more readily consider this, particularly in the era of tenuous vaccine supply and the potential for rapid spread of pandemic flu.

## TAKE HOME MESSAGE

If surveillance has determined that an epidemic is predominantly influenza A, then rapid testing may not be required and rimantadine may be used to treat healthy adults with influenza-like illness. On the other hand, if influenza B predominates, the neuraminidase inhibitors should be recommended. If it is early in the influenza season or if the epidemic is mixed, then rapid testing may help direct the treatment strategy.

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## EBEM TEACHING POINT

*Harm.* Adverse events are commonly reported in studies assessing treatment effects; however, trials are rarely powered to adequately assess harm. The number needed to harm is defined as the number of patients who would need to be treated before 1 adverse effect of the treatment is observed.<sup>5</sup> When data from a single study are used, the number needed to harm is simply the inverse of the absolute risk increase (difference between the adverse event rate in the treatment group and the comparison group). Systematic reviews often provide a point estimate for the RR of the pooled adverse events. If this is the case, an estimate for the number needed to harm can be calculated using the following formula:

$$\text{number needed to harm} = 1/\text{CER}(\text{RR} - 1)$$

where CER=control event rate. As previously reported in this series, using online calculators for this purpose is also a viable and efficient alternative (Visual Rx 2.0, available at <http://www.nntonline.net>).

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