

## FPIN's Clinical Inquiries

### What Is the Best Antiviral Agent for Influenza Infection?

#### Searchable Question

What is the best antiviral treatment for influenza?

#### Evidence-Based Answer

Four antiviral agents have been approved by the U.S. Food and Drug Administration for the treatment of influenza infection: amantadine (Symmetrel), oseltamivir (Tamiflu), rimantadine (Flumadine), and zanamivir (Relenza). No head-to-head trials have compared the effectiveness of these agents, and no direct evidence exists regarding their relative efficacy. In the absence of specific contraindications, amantadine and rimantadine are preferred for use in most patients because these two agents cost less than the other two. Patients with renal insufficiency or a seizure disorder should not take amantadine, and patients with chronic obstructive pulmonary disease or asthma should not take zanamivir. [Strength of recommendation: C]

#### Evidence Summary

The efficacy of each agent has been studied individually. Two systematic reviews showed that amantadine and rimantadine reduced the duration of influenza A symptoms by about one day compared with placebo when the agents were given within 48 hours of symptom onset.<sup>1</sup>

Three systematic reviews found that zanamivir reduced the duration of influenza A and influenza B symptoms by about one day compared with placebo when it was given within 48 hours of symptom onset.<sup>2,3,4</sup> Three systematic reviews also showed that oseltamivir was effective in reducing the duration of symptoms of influenza A and influenza B by one day compared with placebo. However, unlike the other agents, oseltamivir must be given within 36 hours of symptom onset.<sup>2,3,5</sup>

There is insufficient evidence regarding the effects of antiviral agents in reducing serious complications of influenza. One systematic review showed that oseltamivir reduced the incidence of otitis media following influenza in children.<sup>3</sup>

Adverse effects of antiviral agents were addressed in a nonsystematic review by the Centers for Disease Control and Prevention (CDC) in their annual report on influenza.<sup>6</sup> The CDC noted that in a six-week study of healthy adults taking amantadine, rimantadine, or placebo, the incidence of central nervous system (CNS) side effects such as anxiety, insomnia, and difficulty concentrating was 4 percent in the placebo group, 6 percent in the rimantadine group (at 200 mg

daily), and 13 percent in the amantadine group (at 200 mg daily). The CDC noted other studies that found more serious adverse effects such as delirium and seizures, but these adverse effects have occurred primarily in older patients taking amantadine for longer periods, and in patients with renal insufficiency or a comorbid seizure disorder.

The neuraminidase inhibitors (i.e., oseltamivir, zanamivir) are not thought to cause CNS side effects. In one review<sup>2</sup> comparing neuraminidase inhibitors with placebo, patients taking the inhibitors had an incidence of gastrointestinal symptoms of 12.7 percent compared with 4.9 percent in the placebo group (odds ratio [OR], 2.57; 95 percent confidence interval [CI], 1.19 to 5.52). The incidence of overall adverse effects in patients taking neuraminidase inhibitors was 37.6 percent versus 18 percent in the placebo group (OR, 2.59; 95 percent CI, 1.59 to 4.21).<sup>2</sup> Asthma is a contraindication to the use of zanamivir because the latter may induce bronchospasms.<sup>6</sup>

Amantadine and rimantadine treat only influenza type A infection. However, the vast majority of influenza in the United States is type A. During the 2003-2004 influenza season, 99.4 percent of the reported cases were type A.<sup>7</sup> The *accompanying table* compares the four antiviral agents.

<i>Agent</i>	<i>Age approved for treatment</i>	<i>Mechanism of action</i>	<i>Approximate cost*</i>	<i>Influenza viruses inhibited</i>	<i>Usual dosage administration</i>	<i>Route of administration</i>	<i>Side effects</i>
Amantadine (Symmetrel)	Adults and children > one year	Blocks activity of viral M2 protein	\$14 for five-day course (capsule)	A	100 mg twice daily for three to five days (reduced dosage in elderly patients, those with hepatic/renal impairment, and in children one to nine years of age)	Oral (capsule and syrup)	CNS and GI symptoms (dose dependent)
Oseltamivir (Tamiflu)	Adults and children > one year	Neuraminidase inhibitor	\$67 for five-day course (capsule)	A, B	75 mg twice daily for five days (reduced dosage in patients with hepatic/renal impairment and in children one to 13 years of age)	Oral (capsule and powder for suspension)	GI symptoms
Rimantadine (Flumadine)	Adults and children > one year	Blocks activity of viral M2 protein	\$22 for five-day course (tablet)	A	100 mg twice daily for five to seven days (reduced dosage in elderly patients, those with hepatic/renal impairment, and in children one to 10 years of age)	Oral (tablet and syrup)	CNS and GI symptoms

Zanamivir (Relenza)	Adults and children > seven years	Neuraminidase inhibitor	\$57 for one inhaler, five-day course	A, B	Two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily for five days	Oral inhalation (blisters of powder for inhalation using the Diskhaler device)	Bronchospasm in patients with COPD or asthma
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CNS = central nervous system; GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

\*-Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2004.

### Recommendations from Others

The CDC Advisory Committee on Immunization Practices (ACIP) recommends administration of one of the four antiviral agents within two days of influenza symptom onset. If given within this time period, these agents can reduce the duration of uncomplicated influenza in otherwise healthy adults. None of the four agents has been demonstrated to be effective in preventing serious influenza-related complications. The ACIP warns that the use of antiviral agents should not be considered a substitute for influenza vaccination.<sup>6</sup>

### Clinical Commentary

Because the four antiviral agents have similar efficacy, the family physician should consider cost, side effect profiles, spectrum of coverage, and patient's age when selecting an agent. Amantadine and rimantadine are less expensive and have a side effect profile similar to that of placebo. However, the use of amantadine should be avoided in patients 65 years and older, and in patients with renal insufficiency or a seizure disorder. Patients with asthma should not receive zanamivir. Although amantadine and rimantadine are limited in their spectrum of coverage, this is a relatively minor issue. Influenza type B is a mild illness and is not associated with epidemic outbreaks in the United States.

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The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

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