# Antiviral medications for influenza

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## Clinical question

**Do the neuraminidase inhibitors (NIs) oseltamivir or zanamivir improve clinical outcomes in influenza?**

## Bottom line

**Biased, poor-quality, mostly unpublished evidence suggests that oseltamivir and zanamivir shorten the duration of influenza symptoms by 0.6 to 0.7 of a day. Pneumonia and hospitalizations are not decreased.**

## Evidence

Three 2014 systematic reviews of placebo-controlled RCTs (including >160000 pages of previously unreleased clinical study reports)[1-3] found the following when treating otherwise healthy adults with influenza or influenzalike illness with oseltamivir (11 RCTs)[1,2] or zanamivir (14 RCTs)[1,3]:

- Time to symptom improvement was 0.6 to 0.7 days (about 10%) better[1-3]; the benefit of zanamivir was similar to "relief medications" (like acetaminophen).[1,3]
- There was no benefit for pneumonia (x-ray scan confirmed)[1-3] and hospitalizations were not reported[1,3] or there was no benefit.[1,2]
- Adverse events included the following:
  -For oseltamivir,[1,2] the number need to harm was 28 for nausea and 22 for vomiting.
  -Postmarketing surveillance reports (frequency unknown) identified bronchospasm with zanamivir[4] and delirium and self-injury with oseltamivir.[5]

A 2015 systematic review[6] concluded adults receiving oseltamivir had faster symptom alleviation, and fewer lower respiratory tract complications and hospitalizations.

- The review used similar studies[1,2] but the conclusion was based on a subgroup with documented influenza.
- The review was funded by, and 2 authors had pre-existing financial affiliations with, the manufacturer of oseltamivir.

From 26 systematic reviews,[7] authors with financial conflicts of interest were 5 times more likely to report benefits of NI use (this includes a systematic review of cohort studies from the 2009-2010 pandemic suggesting that NIs decreased mortality in hospitalized patients[8]) and less likely to report on publication bias and the quality of included studies.

- Other concerns[1]: unpublished protocols; inconsistent outcome definition; "placebos" with potential adverse effects; and incomplete reporting (eg, missing symptom cards).

## Context

- Oseltamivir sales are >$18 billion, half from government and company stockpiling. Most have not been used.[9]
- The NIs are not recommended if symptoms have lasted longer than 48 hours.[4,5] Zanamivir is contraindicated in asthma and COPD.[4] There is limited evidence for oseltamivir in underlying cardiac or respiratory disease.[5]
- Limited data suggest NIs are likely safe in pregnancy,[10] but the manufacturers do not recommend (zanamivir)[4] or conclude that there are insufficient data and to use them only when the potential benefit justifies the potential risk to the fetus (oseltamivir).[5]

## Implementation

Headache or muscle aches do not reliably differentiate influenza from other respiratory infections. Cough with fever might have the greatest diagnostic value,[11] but knowledge of current local influenza rates is more important. In outbreaks, 79% of patients with fever and cough have influenza,[12] but influenza accounts for only 10% of identified respiratory pathogens in a typical winter.[13] Trials of NIs generally exclude the very young, the old, and those with comorbidity. Targeting those at greatest risk of complications during influenza outbreaks might provide greater utility. High-quality trials enrolling such patients are needed.

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