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Biased, poor-quality, mostly unpublished evidence suggests that oseltamivir and zanamivir shorten the duration of influenza symptoms by 0.6 to 0.7 of a day.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%) better1-3; 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 reported1-3 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 zanamivir4 and delirium and self-injury with oseltamivir.5

A 2015 systematic review6 concluded adults receiving oseltamivir had faster symptom alleviation, and fewer lower respiratory tract complications and hospitalizations.
- The review used similar studies1,2 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 patients8) and less likely to report on publication bias and the quality of included studies.
- Other concerns1: unpublished protocols; inconsistent outcome definition; “placebos” with potential adverse effects; and incomplete reporting (eg, missing symptom cards).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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The opinions expressed in Tools for Practice articles are those of the authors and do not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.

References