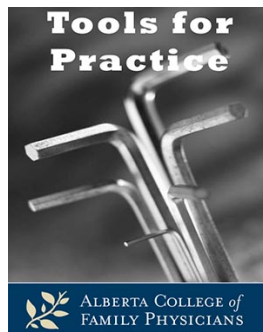


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## Anti-virals for Flu: Looking for evidence for “Stockpile, store, expire, repeat”

**Clinical Question: Do neuramidase inhibitors (NIs) oseltamivir (Tamiflu®) and/or zanamivir (Relenza®) improve clinical outcomes in healthy patients with influenza or influenza-like illness?**

**Bottom-Line: Biased, poor quality, mostly unpublished evidence demonstrates that oseltamivir and zanamivir shorten the duration of influenza symptoms by ~1/2 a day. Objectively defined pneumonia or hospitalizations are not decreased.**

### Evidence:

- 2014 systematic reviews (three publications) of randomized, placebo-controlled trials (RCTs) including >160,000 pages of previously unreleased clinical study reports.<sup>1-3</sup>
  - Treating influenza-like illness or influenza in primarily healthy adults, oseltamivir (11 RCTs)<sup>1,2</sup> and zanamivir (14 RCTs):<sup>1,3</sup>
    - Time to symptom improvement 0.6-0.7 days (~10%) better.<sup>1-3</sup>
      - Zanamivir benefit similar to “relief medications” (like acetaminophen/paracetamol).<sup>1,3</sup>
    - Pneumonia (x-ray confirmed): No benefit.<sup>1-3</sup>
    - Hospitalizations: No benefit<sup>1,2</sup> or not reported.<sup>1,3</sup>
    - Adverse events:
      - Oseltamivir:<sup>1,2</sup>
        - Number Need to Harm: Nausea=28, vomiting=22.
      - Post-marketing surveillance reports (frequency unknown):
        - Zanamivir: Bronchospasm.<sup>4</sup>
        - Oseltamivir: Delirium and self-injury.<sup>5</sup>
  - 2015 systematic review<sup>6</sup> concluded adults receiving oseltamivir had faster symptom alleviation, fewer lower respiratory tract complications and hospitalizations.
    - Used similar studies<sup>1,2</sup> but conclusion based on subgroup of documented influenza.
    - Review funded by, and two authors had pre-existing industry financial affiliations, with manufacturer of oseltamivir.
  - From 26 systematic reviews, authors with financial conflicts of interest were:<sup>7</sup>
    - Five times more likely to report benefits of NI use.
      - This includes a systematic review of cohort studies from the 2009-10 pandemic suggesting that NIs decrease mortality in hospitalized patients.<sup>8</sup>
    - Less likely to report on publication bias and quality of included studies.

- Other concerns (beyond publication bias):<sup>1</sup> Not publishing protocols; inconsistent outcome definition; using “placebos” with potential adverse effects; incomplete reporting (example missing symptom cards).

**Context:**

- Since 1999, oseltamivir sales are >\$18 billion, half from governments and company stockpiling. Most have never been used.<sup>9</sup>
- NIs: Not recommended if symptoms >48 hours.<sup>4,5</sup>
  - Zanamivir: Contraindicated: Asthma or COPD.<sup>4</sup>
  - Oseltamivir: Limited evidence: underlying cardiac or respiratory disease.<sup>5</sup>
- Limited data suggests NIs likely safe in pregnancy<sup>10</sup> although makers of:
  - Zanamivir don't recommend in pregnancy.<sup>4</sup>
  - Oseltamivir conclude insufficient data; only use when potential benefit justifies potential risk to fetus.<sup>5</sup>

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