Systematic review and economic decision modelling for the prevention and treatment of influenza A and B: neuraminidase inhibitors for prevention


CRD summary
This review assessed the prophylactic use of oseltamivir and zanamivir for the prevention of influenza A and B. The authors concluded that both drugs may have potential for preventing influenza, but there are significant gaps in the evidence base. The authors appropriately highlighted the need for further research and discussed limitations in the evidence presented. These conclusions are likely to be reliable.

Authors' objectives
This abstract addresses the prophylactic use of neuraminidase inhibitors for the prevention of influenza A and B. Systematic reviews pertaining to the use of neuraminidase inhibitors for the treatment of influenza A and B, and for the use of amantadine hydrochloride for the treatment and prevention of influenza A, are summarised in other DARE abstracts.

The authors' objective was to assess the effectiveness of two neuraminidase inhibitors, oseltamivir and zanamivir, for the prevention of influenza A and B.

Searching
MEDLINE, EMBASE and the Science Citation Index (all from inception to December 2001), and PubMed and HEED were searched; the search terms were reported. The search findings were checked against 14 named registers and online databases, and the contents and archives of 17 named journals were also searched (further details were given in the report). In addition, the reference lists of identified articles, a named textbook, two relevant reports from the National Institute for Clinical Excellence, and personal databases were checked. Details of additional studies were sought from two pharmaceutical companies. Information on the studies had to have been available in English.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Randomisation could be at the group or individual level.

Specific interventions included in the review
Studies of the prophylactic use of oseltamivir and inhaled zanamivir were eligible for inclusion. Treatment arms of intranasal zanamivir were excluded. The included studies used inhaled zanamivir (5 mg twice daily, or 10 mg once or twice daily, for 5 to 28 days) and oseltamivir (75 mg once or twice daily for 1 to 6 weeks). The included studies assessed the following different prevention strategies: outbreak prophylaxis in the elderly in a residential home; seasonal prophylaxis in a residential home; seasonal prophylaxis in a healthy population; and post-exposure prophylaxis in households.

Participants included in the review
Studies of healthy and high-risk adults and children, and elderly individuals in a residential home setting, were eligible for inclusion. The review defined 'high-risk' as patients of any age with concurrent disease of sufficient severity to require regular medical follow-up, or otherwise healthy patients aged 65 years or older. The included studies were undertaken in different populations of patients, some of whom had already been vaccinated against influenza; the vaccination rates ranged from 9 to 80% among oseltamivir studies, and from 0 to 16% among zanamivir studies.

Outcomes assessed in the review
The primary outcome of interest was the number of individuals with laboratory confirmed symptomatic influenza. Additional outcomes were treatment-related adverse events and early withdrawals from studies.
How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each study was assigned a quality score, using the Jadad scale to assess randomisation, blinding and the reporting of withdrawals. The scale ranged from 1 (lowest) to 5 (highest). The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Data were extracted for the review using a data extraction form, but the authors did not state how many reviewers performed the data extraction. For each study, the number of individuals in each treatment group with an outcome of interest was extracted and used to derive an odds ratio (OR) with 95% confidence interval (CI).

Methods of synthesis
How were the studies combined?
For efficacy data, the studies were combined using a random-effects meta-analysis where sufficient data were available. A pooled OR and 95% CI were calculated separately for intention-to-treat (ITT) populations for each patient subgroup, for all patients and for influenza positive patients, and for laboratory confirmed influenza A and B. For adverse events and withdrawals, the data for each treatment arm were pooled separately on the log odds scale and converted to the percentage scale. The studies were grouped by specific drug and by prevention strategy. Data from different prevention strategies were only combined for the reporting of adverse events and withdrawals. The studies were generally combined in a narrative.

How were differences between studies investigated?
Differences between the populations and interventions were taken into account when grouping the studies. There were insufficient data to perform a sensitivity analysis to examine the effects of study quality and publication status on the results.

Results of the review
Eight RCTs were included in the review. Four RCTs assessed zanamivir (n=2,659) and four RCTs assessed oseltamivir (n=3,062).

For zanamivir, two studies scored 3 on the Jadad scale and two scored 4. For oseltamivir, two studies scored 4 on the Jadad scale and two scored 5. Some studies made no allowance for clustering in the analysis.

Zanamivir.

Outbreak prophylaxis in the elderly in a residential home setting (1 RCT, n=280): only 3 patients (2%) developed laboratory confirmed symptomatic influenza. Thus, the results were inconclusive.

Seasonal prophylaxis in a healthy population (1 RCT, n=1,107): zanamivir significantly reduced the likelihood of contracting influenza by 69% (95% CI: 36, 86).

Post-exposure prophylaxis in the household setting (2 RCTs, n=1,125): zanamivir significantly reduced the likelihood of contracting influenza (OR 0.19, 95% CI: 0.09, 0.38), based on ITT data from 1,125 patients in two RCTs. A similar reduction was found for laboratory confirmed influenza (OR 0.18, 95% CI: 0.07, 0.43), based on 195 patients in one RCT. The duration of treatment was 5 days in one RCT and 10 days in the other RCT.

Oseltamivir.

Seasonal (long-term) prophylaxis in a frail elderly population in a residential home setting (1 RCT, n=988): oseltamivir significantly reduced the likelihood of contracting influenza for all patients, (OR 0.08, 95% CI: 0.01, 0.61) and for...
previously vaccinated patients (OR 0.09, 95% CI: 0.001, 0.67).

Seasonal prophylaxis in healthy adults (2 RCTs, n=1,039): oseltamivir significantly reduced the likelihood of contracting influenza (OR 0.26, 95% CI: 0.08, 0.84).

Post-exposure prophylaxis in households (1 RCT, n=1,370): oseltamivir significantly reduced the likelihood of contracting influenza for all patients (ITT analysis; OR 0.10, 95% CI: 0.04, 0.29) and for influenza-positive patients (OR 0.10, 95% CI: 0.03, 0.34).

Adverse events.

Studies of both drugs used different definitions for adverse events, and it was difficult to distinguish adverse events from complications. For zanamivir versus placebo, similar percentages of patients reported adverse events in each treatment group: 7.5% (95% CI: 6.2, 9.2) with zanamivir versus 7.8% (95% CI: 6.4, 9.7) with placebo, based on 2,553 patients in three RCTs. The number of individuals with at least one adverse event was not reported in any trial of oseltamivir.

Withdrawals. Low rates of withdrawal were found for zanamivir (1.3%, 95% CI: 0.9, 2.0) versus placebo (2.4%, 95% CI: 1.7, 3.8), based on 2,265 patients in two RCTs, and for oseltamivir (2.5%, 95% CI: 1.7, 3.8) versus placebo (3.2%, 95% CI: 2.2, 4.9), based on 1,994 patients in two RCTs.

Cost information
The review included a cost-effectiveness analysis of prophylaxis with amantadine, oseltamivir, zanamivir and vaccine. The review found that in the base-case analysis of prophylaxis, oseltamivir and zanamivir were dominated by vaccine. For oseltamivir, the uncertainty analysis suggested a probability of 3% of an incremental cost per quality-adjusted life-year (QALY) below £30,000 in residential populations. None of the other population studies had a probability of greater than 1% of an incremental cost per QALY below £30,000. For zanamivir, none of the study populations were found to have a probability of greater than 1% of an incremental cost per QALY below £30,000.

Authors’ conclusions
The studies suggested that oseltamivir and zanamivir have the potential to prevent influenza. However, there were significant gaps in the evidence base, including no evidence in children.

CRD commentary
The review question was clear and the inclusion criteria appeared appropriate. The search was extensive and attempts were made to limit publication bias. However, only English publications were included, thus introducing language bias. The methods used to select studies, assess quality and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Relevant information on the included studies was presented. The studies were appropriately grouped by setting and target population, and combined in a narrative. Only data from similar populations in comparable settings were pooled using meta-analysis. Where this was done, forest plots allowed an examination of statistical heterogeneity.

The evidence presented appears to support the authors’ conclusion about the potential benefit of oseltamivir and zanamivir. The authors correctly highlighted the potential for bias resulting from publication bias, owing to the unavailability of data from some trials, and issues about data quality.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors highlighted the paucity of research in this field. The authors stated that further research into the effectiveness of neuraminidase inhibitors in preventing influenza in elderly people in residential care is required, and that no evidence was found in child populations.
Funding
NHS R&D Health Technology Assessment (HTA) Programme, project number 01/47/01.

Bibliographic details

Original Paper URL
http://www.hta.ac.uk/project.asp?PjtId=1299

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antiviral Agents /classification /economics /therapeutic use; Cost-Benefit Analysis; Decision Support Techniques; Influenza Vaccines /administration & dosage /economics; Orthomyxoviridae Infections /classification /drug therapy /economics /prevention & control; Quality-Adjusted Life Years; Treatment Outcome

AccessionNumber
12004008832

Date bibliographic record published
31/08/2005

Date abstract record published
31/08/2005

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.