Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation

CRD summary
This well-conducted review concluded that zanamivir and oseltamivir were effective in reducing symptom duration, but the clinical significance of the modest effect sizes was debatable. Evidence relating to complication rates and adverse events was inconsistently reported across trials; from the evidence available, there was limited impact of either drug. The review's conclusions are likely to be reliable.

Authors' objectives
To determine the clinical effectiveness and safety of oseltamivir and zanamivir for the treatment of naturally acquired seasonal influenza.

Searching
Eleven databases that included MEDLINE, EMBASE, CINAHL, BIOSIS Previews, DARE, the Cochrane Library and Health Technology Assessment Database were searched, without language restriction, from 2001 to November 2007. Studies before 2001 were identified from a previous systematic review. Search terms were reported. Various sources were searched for unpublished research. Reference lists of relevant publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared oseltamivir or zanamivir to placebo, best symptomatic care, or each other, administered in accordance with their respective UK licences, were eligible for inclusion. Trials of prophylaxis or those conducted during a pandemic or widespread epidemic of a new strain of influenza were excluded.

The review outcomes were time to alleviation of symptoms and normal activity, complications, hospitalisation, antibiotic use, mortality and adverse events.

The majority of included trials recruited healthy adults or at-risk populations (those with comorbid conditions and the elderly). Where reported, participants' age ranged from one to 99 years, the proportion of males ranged from 21 to 99%, and the delay from onset of symptoms to initiation of treatment was up to 36 or 48 hours. Most included trials defined influenza-like illness; the definition varied across trials and some did not specify a temperature.

Two reviewers independently assessed studies for inclusion. Any disagreement was resolved by consensus or a third reviewer.

Assessment of study quality
The quality of RCTs was assessed by one reviewer using the following criteria: randomisation; allocation concealment; blinding; reporting of eligibility criteria; recruitment of a representative population; comparability of groups at baseline; use of a power calculation; and losses to follow-up. Results were checked by a second reviewer; disagreement was resolved by consensus or a third reviewer.

Data extraction
For dichotomous outcomes, event rates were extracted to enable the calculation of odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, the median and standard deviation (SD) were extracted to enable the calculation of median differences with 95% confidence intervals. Where standard errors (SEs) of the medians were not available, they were estimated from 95% confidence intervals using the delta method. Pharmaceutical companies were contacted for additional data.

Data were extracted by one reviewer and checked by a second reviewer. Any disagreement was resolved by consensus or a third reviewer.
Methods of synthesis
Pooled odds ratios and weighted median differences (WMDs), with 95% confidence intervals, were calculated using a random-effects model where there were more than four trials, otherwise a fixed-effect model was employed. Heterogeneity was assessed using the X² test and I² statistic. Using continuous outcomes, an indirect comparison was undertaken using placebo as the common comparator.

Subgroup analyses were performed on healthy adults, children, at-risk, and elderly populations. Separate analyses were conducted for those with influenza-like illnesses (intention-to-treat) and those with confirmed influenza.

Results of the review
Twenty-nine RCTs (n=15,096 participants) were included in the review. Methodological quality varied between trials. Twenty-five trials were double-blinded. Thirteen trials reported an appropriate method of randomisation. Only eight trials reported allocation concealment. The duration of follow-up ranged from five to 28 days; only 15 trials had over 95% follow-up.

Comparison with placebo
Zanamivir significantly reduced the median time to symptom alleviation in healthy adults with influenza-like illnesses (WMD -0.57 days, 95% CI -1.07 to -0.08; six RCTs), and the overall at-risk population (WMD -0.98 day; 95% CI -1.84 to -0.11; seven RCTs).

Oseltamivir significantly reduced the median time to symptom alleviation in healthy adults with influenza-like illnesses (WMD -0.55 days, 95% CI -1.05 to -0.14; four RCTs), but not the overall at-risk population (WMD -0.59 days, 95% CI -1.70 to 0.54; three RCTs).

No significant heterogeneity was observed for these outcomes. The limited evidence available for influenza-related complication rates, and the adverse events associated their use, showed little overall impact of either drug on these outcomes. Results for time to normal activity, for those infected with influenza, and for a range of patient subgroups were also reported.

Indirect analysis of interventions:
Oseltamivir had a higher probability of being the better treatment for healthy adults, and zanamivir for at-risk populations.

Cost information
Cost-effectiveness estimates were more favourable in at-risk populations compared with healthy populations. For at-risk populations, the incremental cost-effectiveness ratio estimates were robust for a wider range of alternative assumptions (below £20,000 per quality-adjusted life-year for most scenarios).

Authors' conclusions
Zanamivir or oseltamivir treatment was effective in reducing symptom duration; the clinical significance of the modest effect sizes was debatable. There was limited evidence for the effect of these drugs on influenza-related complications, or on adverse events associated with their use.

CRD commentary
The review addressed a clear research question supported by appropriate and well-defined inclusion criteria. The search was extensive and efforts were made to find both published and unpublished studies without language restrictions, which reduced potential for publication and language biases. Sufficient attempts were made to minimise the errors and biases in the review process.

Relevant criteria were used to examine the study quality. Statistical heterogeneity was assessed and appropriate statistical methods were used to pool the results. This review was well conducted and the authors' conclusions are likely to be reliable.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that an adequately powered, well-designed head-to-head trial (with a placebo group and sufficient follow-up) were required to assess the clinical and cost-effectiveness of antiviral drugs in at-risk populations. They also stated that well-designed observational studies could be considered to evaluate the clinical course of influenza in terms of complications, hospitalisation, mortality and quality of life.

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the reliability of the review and the conclusions drawn.