Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies


CRD summary
This review evaluated oseltamivir and zanamivir for treatment of influenza virus A or B and amantadine and rimantadine for influenza A. The authors concluded that oral oseltamivir and inhaled zanamivir may provide benefits over no treatment. Their cautious conclusion of low confidence for decision-making seems to be reliable.

Authors' objectives
The primary objective was to evaluate the efficacy and safety of neuraminidase inhibitors (oseltamivir and zanamivir) for treatment of influenza virus A or B and M2 ion channel blockers or adamantanes (amantadine and rimantadine) for treatment of influenza A.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, SIGLE, Chinese Biomedical Literature Database, Panteleimon and LILACS were searched to November 2010. There were no language restrictions. Unpublished data were sought from the World Health Organisation, pharmaceutical companies, United States Food and Drug Administration, European Medicines Agency, Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control. Reference lists of relevant studies and reviews were scanned for further studies. Search terms were reported.

Study selection
Studies that were eligible for inclusion were observational studies in any population that compared antiviral drugs (oseltamivir, zanamivir, amantadine and rimantadine of any dose and by any route except intravenously) to no antiviral treatment or with another antiviral drug for treatment of laboratory-confirmed influenza or unconfirmed influenza-like illness. Studies without an independent comparison were included. Randomised controlled trials, studies with fewer than 25 patients and studies that evaluated antiviral chemoprophylaxis were excluded.

Outcomes of interest were: death; hospitalisation; intensive care unit admission; mechanical ventilation and respiratory failure; duration of hospitalisation; duration of signs and symptoms; time to return to normal activity; complications; critical and important adverse events (defined in the paper); influenza viral shedding; and antiviral resistance.

The comparisons analysed were oral oseltamivir, inhaled zanamivir and oral amantadine compared with no antiviral therapy, and oral oseltamivir compared with inhaled zanamivir. Details were lacking on drug dose and patient characteristics. There were no studies of rimantadine versus no antiviral therapy.

Two reviewers independently selected the studies for inclusion. Disagreements were resolved by discussion or with the involvement of a third reviewer.

Assessment of study quality
Study quality was assessed using the Newcastle-Ottawa Scale of selection and comparability of study groups and ascertainment of the exposure or outcome of interest. GRADE criteria were used to assess the overall level of confidence in the effect estimate.

Two reviewers independently applied the quality criteria. Disagreements were resolved by consensus.

Data extraction
Data were extracted to enable calculation of odds ratios (OR), mean differences or rate ratios, each with 95% confidence intervals (CI).

Two reviewers independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis
Odds ratios, mean differences or standardised mean differences (SMDs) were pooled in meta-analyses. Random-effects and fixed-effect models were used as appropriate. Inverse variance weighting was used where applicable. Analyses adjusted for confounders were presented separately. Where possible, subgroup analyses were conducted according to age (one to 15 years, 16 to 65 years and ≥65 years), level of risk for complications (low risk, patients admitted to the intensive care unit and immunocompromised patients), influenza type A or B, laboratory-confirmed versus unconfirmed influenza, pandemic or interpandemic influenza, dose of antiviral agent and potential funding conflict. Statistical heterogeneity was assessed with $\chi^2$ and $I^2$ and explored further where $I^2$ was more than 60%.

Results of the review
Seventy-four studies were included in the review. The overall quality of evidence according to GRADE criteria was generally low or very low. The authors stated that there was evidence of confounding, together with selection, reporting and publication biases.

Oral oseltamivir compared with no antiviral therapy: There were 51 studies. Adjusted analysis showed significant differences that favoured oseltamivir for reduced mortality (OR 0.23, 95% CI 0.13 to 0.43; three studies), hospitalisation (OR 0.75, 95% CI 0.66 to 0.84; four studies) and significantly fewer complications in terms of otitis media (OR 0.75, 95% CI 0.64 to 0.87; two studies). Critical adverse events were lower (rate ratio 0.76, 95% CI 0.70 to 0.81; five studies). A reduction in the duration of signs and symptoms was reported (SMD -0.91, 95% CI -1.25 to -0.57; seven studies). Earlier treatment with oseltamivir was associated with significantly better outcomes in terms of hospitalisations (two studies), intensive care unit admissions (five studies) and viral shedding (one study). There was no heterogeneity in any of the above analyses.

Inhaled zanamivir compared with no antiviral therapy: There were five studies. Inhaled zanamivir was associated with significantly shorter symptom duration (SMD -0.90, 95% CI -1.08 to -0.72; five studies, moderate quality evidence) and fewer hospitalisations (not statistically significant; two studies). There were generally more complications with inhaled zanamivir than no treatment. There was no heterogeneity in these analyses.

Direct comparisons of oral oseltamivir and inhaled zanamivir (eight studies) revealed no important differences in key outcomes, although a pooled estimate was not possible for mortality. Analyses that compared oral amantadine (six studies) with no antiviral therapy were based largely on one or two studies.

There was high heterogeneity in some of the other analyses. Further results were presented in the paper.

Authors’ conclusions
Therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. Confidence in the effect estimates to aid decision-making was low to very low.

CRD commentary
The review question was clear. Inclusion criteria were sufficiently detailed. Various data sources were searched. Attempts were made to minimise language and publication biases. The review process was conducted with steps to minimise error and bias at all stages. Appropriate quality criteria were applied, but results were limited to summary detail. Study details were lacking on drug dose and patient characteristics and high heterogeneity in some analyses suggested that statistical pooling might not have been appropriate in certain cases. There appeared to be some discrepancies between text and forest plots.

The authors acknowledged the limitations of this review in terms of reliance on observational data. Their cautious conclusion relating to low confidence for decision-making seems 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 a need for high quality randomised controlled trials that include hospitalised patients with influenza. Future observational studies should be prospective and take steps to minimise selection bias, permit data collection of all prognostic variables and provide standardised and validated assessments of adverse events. Serial
virologic samplings should be performed alongside clinical data collection.

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