Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation

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CRD summary
This review concluded that amantadine, oseltamivir or zanamivir showed some efficacy for seasonal and post-exposure prophylaxis. The results of the review were limited by a paucity of good quality evidence. There was a possibility of error and bias in the review process, but the overall conclusion was likely to be reliable.

Authors’ objectives
To evaluate the clinical and cost effectiveness of antiviral drugs for influenza prophylaxis.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, BIOSIS Previews, CINAHL, DARE, NHS EED, the HTA database, the Office of Health Economics Health Economic Evaluations Database, National Research Register, Science Citation Index, Current Controlled Trials and ClinicalTrials.gov were searched for studies in any language up to July 2007. The search strategy was reported. Studies not reported in English were subsequently excluded. Submissions from manufacturers were also searched.

Study selection
Randomised controlled trials (RCTs) evaluating the effectiveness and safety of amantadine, oseltamivir or zanamivir for seasonal prophylaxis, or prophylaxis post-exposure to either naturally acquired or experimentally induced influenza when compared to each other, a placebo, usual care or no treatment were eligible for inclusion. This abstract considers the results from studies of naturally acquired influenza.

Outcomes of interest were the incidence and severity of influenza, mortality, health-related quality of life (HRQoL), adverse events and complications. Most included studies were of healthy adults or the elderly. Doses and duration of prophylaxis varied across studies. Studies were selected by one reviewer, with recourse to a second reviewer when necessary.

Assessment of study quality
Study quality was assessed by one reviewer in terms of: randomisation; allocation concealment; eligibility criteria; comparability at baseline; blinding; identification of effect modifiers; the use of an ITT analysis; and the proportion of dropouts. The quality assessment was checked by a second reviewer.

Data extraction
The incidence of confirmed influenza in contacts was extracted and a relative risk (RR) with 95% confidence intervals (CI) calculated for each study. The proportion of people adhering to medication and experiencing adverse events was also extracted. Data were extracted by one reviewer and checked by a second reviewer.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Protective efficacy was calculated. Data on adherence and the incidence of adverse events were combined in a narrative synthesis. Study details and results were tabulated. Differences between studies were discussed in the text.

Results of the review
Eighteen studies of naturally acquired influenza met the inclusion criteria: five evaluated amantadine (n=9,671; range 101 to 8,267); five evaluated oseltamivir (n=3,334; range 503 to 955); and eight evaluated zanamivir (n=7,724; range 25 to 3,279). Most information required to assess study quality was not reported in the amantadine trials. Reporting in the oseltamivir and zanamivir trials was substantially better, but the method of randomisation and allocation concealment was still unclear in nine studies. Two oseltamivir trials and six zanamivir trials reported some level of blinding. All
studies had follow-up for at least 80 per cent of participants.

Seasonal prophylaxis: There was no significant impact of amantadine on the incidence of laboratory confirmed influenza in healthy adults compared to placebo (two studies). Significant reductions were reported with oseltamivir (RR 0.27, 95% CI: 0.09, 0.83; two studies, n=1,039) and in one of two zanamivir trials. Oseltamivir significantly reduced the incidence of influenza in the ‘at risk’ elderly (RR 0.08, 95% CI: 0.01, 0.63; one study, n= 548). Zanamivir significantly reduced the incidence of influenza in ‘at-risk’ adults and adolescents (RR 0.17, 95% CI 0.07, 0.44; one study, n=3,363), but not significantly so in the elderly (RR 0.20, 95% CI 0.02, 1.72; one study, n=1,896).

Post-exposure prophylaxis: Two trials of amantadine reported significant reductions in the incidence of post-exposure influenza with treatment compared to placebo. Significant reductions in the incidence of laboratory confirmed influenza were also observed with oseltamivir (RR 0.19, 95% CI: 0.08, 0.45; two studies, n=1,747) and zanamivir (RR 0.21, 95% CI: 0.13, 0.33; three studies, n=2,416) in mixed households after exposure to influenza-like illnesses.

Limited data were available regarding adherence, adverse events and complications; a narrative synthesis is presented for these outcomes. Resistance was also discussed. No data were available for HRQoL or mortality.

Cost information
The incremental cost-utility (ICU) of seasonal influenza prophylaxis was estimated to be £16,630 per quality adjusted life year (QALY) for at-risk children; the ICU for all other subgroups was estimated to be in the range of £38,000 to £428,000 per QALY. The cost-effectiveness of oseltamivir and zanamivir for post-exposure prophylaxis was estimated to be below £30,000 per QALY in unvaccinated children, at-risk adults and the elderly.

Authors’ conclusions
All three antiviral drugs showed some efficacy for seasonal and post-exposure prophylaxis.

CRD commentary
The authors addressed a clear research question with appropriate inclusion criteria. An extensive search was undertaken. However, publication and language bias could not be ruled out. Data extraction and quality assessment were conducted in duplicate, but as study selection was conducted by one reviewer with recourse to a second only when considered necessary, selection bias may have been present. Appropriate criteria were used to assess study quality and results provided for each criterion for each study. The decision to combine most of the results in narrative syntheses seemed appropriate. Where pooled estimates were calculated, these often included only two or three trials. Evidence was lacking for some groups of people.

Although the results of the review were limited by a paucity of good-quality evidence, the overall conclusion was likely to be reliable.

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

Research: RCTs in subgroups where data was lacking, with follow-up periods beyond that of the duration of prophylaxis were required. Head-to-head RCTs in which the clinical effectiveness of amantadine, oseltamivir and/or zanamivir in different subgroups is directly compared were required. Quality of life and the incidence and management of complications needed investigating.

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Bibliographic details

PubMedID
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.