

H1N1 Influenza A (Swine Flu) Alert Center

From Medscape Medical News



## Oseltamivir Efficacy Questioned in Preventing Influenza Complications

Fran Lowry

December 9, 2009 — An updated Cochrane review has called into question the efficacy of neuraminidase inhibitors, including the most commonly used oral agent oseltamivir (*Tamiflu*, Roche Laboratories Inc), in preventing influenza complications in healthy adults.

The results of the review, published online December 8 in the *British Medical Journal*, appear with other articles on oseltamivir that all come to the same conclusion: The evidence for the drug's efficacy in reducing complications in otherwise healthy individuals with pandemic influenza is now uncertain.

According to a statement by the *BMJ*, the results have led to a joint investigation into oseltamivir by *BMJ* and Channel 4 News, based in London, United Kingdom.

Tom Jefferson, MD, from the Acute Respiratory Infections Group, Cochrane Collaboration, Rome, Italy, and colleagues updated a 2005 Cochrane review published in the Cochrane Library.

The researchers selected 20 randomized, placebo-controlled studies of neuraminidase inhibitors in otherwise healthy adults exposed to naturally occurring influenza to determine duration and incidence of symptoms, incidence of lower respiratory tract infections or their proxies, and adverse events.

They focused on oseltamivir because of the greater experience with the drug worldwide.

### Few Trials Judged Adequate Also Had Shortcomings

Of the trials, only 5 were judged adequate by usual Cochrane Collaboration methods, Dr. Jefferson and colleagues write. Most of the trials were at risk for bias resulting from poor descriptions of the methods, no description of losses to follow-up, and blinding.

The authors write that their attempts to deal with these shortcomings failed. Only 3 of the 5 lead authors of the studies on oseltamivir replied to their request for more information. Of these authors, none possessed original data.

Instead, these authors referred them to Roche, oseltamivir's manufacturer. However, the company did not provide the information "as quickly as we needed it to update this review," Dr. Jefferson and colleagues write.

From their analysis, the reviewers found that oseltamivir did not reduce influenza-related lower respiratory tract complications (risk ratio, 0.55; 95% confidence interval, 0.22 - 1.35).

They also found that oseltamivir induced nausea (odds ratio, 1.79; 95% confidence interval, 1.10 - 2.93), that the evidence of rarer adverse events from pharmacovigilance studies was of poor quality, and that adverse events may have been underreported.

"Neuraminidase inhibitors have modest effectiveness against the symptoms of influenza in otherwise healthy adults. The drugs are effective postexposure against laboratory confirmed influenza, but this is a small component of influenza-like illness, so for this outcome neuraminidase inhibitors are not effective," Dr. Jefferson and colleagues conclude.

Oseltamivir may be regarded as optional for reducing the symptoms of seasonal influenza, they add. "Paucity of good data has undermined previous findings for oseltamivir's prevention of complications from influenza. Independent randomized trials to resolve these uncertainties are needed."

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In a related article, Peter Doshi, a doctoral student at Massachusetts Institute of Technology in Cambridge, and a coauthor of the updated Cochrane review, writes that his team of reviewers had been trying to obtain data to verify claims that oseltamivir lowers serious complications of influenza since August 2009.

### **Evidence Is Fragmented, Inconsistent, Contradictory**

"We failed, but in failing discovered that the public evidence base for this global public health drug is fragmented, inconsistent, and contradictory. We are no longer sure that oseltamivir offers a therapeutic and public health policy advantage over cheap, over the counter drugs such as aspirin," he writes.

Mr. Doshi writes that the review team's suspicions were aroused after a Japanese pediatrician, Keiji Hayashi, MD, pointed out that their previous review, which had found that oseltamivir was effective in reducing pneumonia and other important complications of influenza, was based on a single peer-reviewed study by Kaiser and colleagues.

It turns out that the Kaiser study, which was a meta-analysis of 10 manufacturer-funded trials, included just 2 studies that were published in peer-reviewed journals. When the Cochrane reviewers tried to verify the data from the 8 unpublished trials, they found inconsistencies in the evidence for oseltamivir's effectiveness and safety.

Roche funded the Kaiser meta-analysis.

Mr. Doshi said the Kaiser paper was dropped from their new analysis. "The previous Cochrane review placed its trust in publications and included Kaiser's unpublished data, but to do so once again, despite our inability to obtain data sufficient to perform an independent analysis, would have shifted our position from that of trust in publication to that of trust in secrecy."

He also called into question US Food and Drug Administration's safety reporting rules. Manufacturers must report adverse events, but only if they occur in the United States. "In the case of oseltamivir, considering that 75% of global consumption has occurred in Japan, this has important implications for our knowledge of its safety," Mr. Doshi writes.

### **Treatment With Oseltamivir Unlikely to be Clinically Important**

Nick Freemantle, PhD, and Melanie Calvert, MD, from the University of Birmingham, United Kingdom, were invited by *BMJ* to review the observational studies provided to the Cochrane reviewers by Roche. They said that in general, the studies support the conclusion that oseltamivir may reduce the incidence of complications of influenza in otherwise healthy adults, but as such events are rare, treatment with oseltamivir for most people is not likely to be clinically important.

They had several criticisms of the studies and said the studies were difficult to interpret. "Differences in baseline comorbidity or geographical distribution were present in several studies. It seems likely that some patients were included in more than one study, which undermines the ability of these studies to provide independent estimates," the authors write.

"We have remarkably few resources in this country to spend on pharmaceuticals on health and it's surprising to see such widespread use of oseltamivir. But I suppose that once you've gone and bought lots of doses then it's a bit like the situation with gun control in the US. If you have a gun in the house it's much easier to use it. But it does not mean it's the right thing to do," Dr. Freemantle said in a statement to *BMJ*.

### **Review Calls Entire Process Into Question**

Fiona Godlee, MD, Editor-in-Chief of *BMJ*, and Mike Clarke, MD, Director of the UK Cochrane Centre, say the updated review is important because it calls into question "not only the effectiveness of oseltamivir but the whole system by which drugs are evaluated, regulated and promoted."

In her editorial, Dr. Godlee writes that the claims of the efficacy of oseltamivir, based on an analysis of 10 drug company trials, have formed a key part of decisions to stockpile the drug and made it widely available.

It was only after questions from the *BMJ* and Channel 4 News that Roche agreed to make full study reports available on a password-protected site, she writes.

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"It can't be right that the public should have to rely on this sort of detective work by academics and journalists to patch together the evidence for such a widely prescribed drug. Individual patient data from all trials of drugs should be readily available for scientific scrutiny," Dr. Godlee concludes.

In its reply, Roche says it has provided full responses to all questions from the *BMJ* and Channel 4, which "should leave no doubt about the

**such a widely prescribed drug.**

high integrity of the data, publications, and interactions between Roche and independent investigators."

All reports were written to the standards of the regulatory authorities of Europe, the United States, and Japan, and have been accepted by all for licensing purposes. Roche has "willingly shared data and reports with numerous other eligible individuals and groups," writes James Smith, MD, International Medical Leader, Tamiflu, for Roche.

He voices concern that the Cochrane review team "chose to follow-up their inquiries through a television company rather than by approaching the manufacturer directly...it is unclear to us why Dr. Jefferson would adopt this approach, particularly given that he was a paid ad hoc consultant to Roche working on flu and oseltamivir between 1997 and 1999. During that period he worked closely with Roche experts, many of whom are still in the company, and he would therefore not have had difficulty in contacting them directly to discuss his requirements."

Dr. Smith ends by stating: "Why Dr. Jefferson and the *BMJ* chose to pursue their scientific enquiries through commercial television remains to be clarified."

*Dr. Jefferson has reported he has received support from the UK National Institute for Health Research and the Australian National Health and Medical Research Council and that he was a paid ad hoc consultant to Roche from 1997 to 1999. Peter Doshi has reported he has no relevant financial relationships. Dr. Nick Freemantle and Dr. Melanie Calvert have reported that the BMJ helped them access 3 articles not available through their university library and that they supervise a PhD student who is supported and employed by Roche. Dr. Godlee has reported that she has published a number of articles critical of the drug industry and supports the idea that drugs should be evaluated by independent third parties rather than directly or indirectly by the drug's producers. As editor of the BMJ, she is a member of the International Committee of Medical Journal Editors and reports that the BMJ Group receives a proportion of its revenue from drug company advertising and sponsorship. Dr. Mike Clarke has reported that he is active in the Cochrane Collaboration and has a fixed-term contract with the National Institute for Health Research. Dr. Smith is international medical leader, Tamiflu, F Hoffmann-La Roche.*

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## **Authors and Disclosures**

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Session data

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