Cochrane for Clinicians

Putting Evidence into Practice

Neuraminidase Inhibitors for Influenza Treatment and Prevention in Healthy Adults

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Cayley presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www.cochrane.org/reviews/en/ab001265.html.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 239.

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A collection of Cochrane for Clinicians published in *AFP* is available at http://www.aafp.org/afp/cochrane.

Clinical Scenario

A previously healthy woman presents in the middle of the influenza season with a one-day history of cough and a fever of 101°F (38.3°C). She asks if there is a medication to help treat her illness and to prevent her family members from getting ill.

Clinical Question

Should neuraminidase inhibitors be used for preventing or treating influenza in healthy adults?

Evidence-Based Answer

Although neuraminidase inhibitors can reduce the risk of contracting symptomatic, confirmed influenza and reduce the time to recovery for those with laboratory-confirmed influenza, they are not effective for reducing the risk of influenza-like illness or asymptomatic influenza infection in healthy adults. It is uncertain whether neuraminidase inhibitors prevent respiratory complications of influenza.[1] (Strength of Recommendation = A, based on consistent, good-quality patient-oriented evidence)

Practice Pointers

The neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) have been available for more than 10 years for the prevention and treatment of influenza. Because influenza A and B viruses depend on neuraminidase for viral replication, neuraminidase inhibitors are effective against both types. Older adamantanes (amantadine and rimantadine [Flumadine]) are only effective against influenza A subtypes. Neuraminidase inhibitors were recommended for the treatment of influenza-like illness and 2009 H1N1 influenza (swine flu) during the 2009 to 2010 influenza season, and for prophylaxis of exposed persons, based on resistance of 2009 H1N1 influenza to adamantanes.[2]

The authors of this Cochrane review[1] set out to update information on the effectiveness of neuraminidase inhibitors against influenza from their earlier Cochrane review on this subject,[3] and to address the risk of adverse events from treatment with neuraminidase inhibitors. Consistent with the earlier review, they found evidence supporting the effectiveness of neuraminidase inhibitors for preventing symptomatic, laboratory-confirmed influenza; reducing household transmission of influenza; reducing sick days in those who contracted influenza from household members; and reducing time to alleviation of symptoms in those with influenza. However, neuraminidase inhibitors did not prevent influenza-like illness (i.e., constitutional symptoms and fever with cough or sore throat) or asymptomatic influenza infection.

The earlier Cochrane review reported that oseltamivir prevented lower respiratory tract complications.[3] The authors noted that this conclusion depended heavily on one review that included unpublished industry data. When they were unable to obtain these data from the manufacturer, the authors excluded this review from analysis for the current Cochrane review.[1] They found the remaining evidence inadequate to demonstrate whether neuraminidase inhibitors reduce complications of influenza, such as pneumonia, bronchitis, or other respiratory infections requiring treatment with antibiotics. This issue was addressed by one of the authors in a separate commentary.[4]

Cochrane Abstract

Background: Neuraminidase inhibitors are recommended for use against influenza and its complications in interpandemic years and during pandemics.

Objectives: To assess the effects of neuraminidase inhibitors in preventing and treating influenza, its transmission, and its complications in otherwise healthy adults, and to estimate the frequency of adverse effects.

Search Strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2009, issue 3), which contains the Acute Respiratory Infections Group's specialized register; Medline (1950 to August 2009); and EMBASE (1980 to August 2009).

Selection Criteria: Randomized controlled trials (RCTs) or quasirandomized, placebo-controlled trials of neuraminidase inhibitors in healthy adults exposed to naturally occurring influenza.

Data Collection and Analysis: Two review authors independently applied inclusion criteria, assessed trial quality, and extracted data. They structured the comparisons into prophylaxis, treatment, and adverse events, with further subdivision by outcome and dose.

Main Results: The authors identified four prophylaxis, 12 treatment, and four postexposure prophylaxis trials. In prophylaxis compared with placebo, neuraminidase inhibitors had no effect against influenza-like illnesses (risk ratio [RR] ranging from 1.28 for oral oseltamivir [75 mg daily] to 0.76 for inhaled zanamivir [10 mg daily]). The effectiveness of oral oseltamivir against symptomatic influenza was 76 percent at a dosage of 75 mg daily, and 73 percent at a dosage of 150 mg daily. Inhaled zanamivir (10 mg daily) performed similarly. Neither neuraminidase inhibitor had a significant effect on asymptomatic influenza. Oseltamivir induced nausea (odds ratio = 1.79; 95% confidence interval [CI], 1.10 to 2.93). Oseltamivir for postexposure prophylaxis had an effectiveness of 58 and 84 percent in two trials for households. Zanamivir performed similarly. The hazard ratios for time to alleviation of symptoms were in favor of the treated group at 1.20 (95% CI, 1.06 to 1.35) for oseltamivir and 1.24 (95% CI, 1.13 to 1.36) for zanamivir. Because of the exclusion of a review of mainly unpublished trials of oseltamivir, insufficient evidence remained to reach a conclusion on the prevention of complications requiring antibiotics in influenza cases (RR = 0.57; 95% CI, 0.23 to 1.37). Analysis of the U.S. Food and Drug Administration and Japan's Pharmaceuticals and Medical Devices Agency regulators' pharmacovigilance dataset revealed incomplete reporting and description of harms, preventing the authors from reaching firm conclusions on the central nervous system toxicity of neuraminidase inhibitors.

Authors' Conclusions: Numerous inconsistencies detected in the available evidence, followed by an inability to adequately access the data, has undermined confidence in the authors' previous conclusions for oseltamivir. Independent RCTs to resolve these uncertainties are needed.

Two other limitations in published data affected the authors' ability to fully appraise the risk-benefit balance for using neuraminidase inhibitors to treat influenza.[1] First, they were unable to completely assess rates of severe adverse events, including psychiatric events, because of inconsistencies in reporting of adverse events across databases. Second, they noted that some of the trials demonstrating the effectiveness of neuraminidase inhibitors had an unusually high prevalence of influenza among participants, which might give overly optimistic estimates of effectiveness.

Neuraminidase inhibitors appear effective for reducing sick days in those with influenza and those who contracted influenza from persons in their household. However, neuraminidase inhibitors do not prevent influenza-like illness during influenza season or asymptomatic infection with influenza virus, and there is insufficient evidence to determine whether they meaningfully reduce the risk of influenza respiratory complications requiring antibiotics. Thus, it is unclear if neuraminidase inhibitors can actually decrease the spread of influenza and the rate of serious complications during an epidemic or pandemic, or if they serve mainly to relieve symptoms in those infected.

The Advisory Committee on Immunization Practices has recommended annual influenza vaccination to include all persons who are six months and older,[5] and the evidence in this Cochrane review reinforces the importance of relying on vaccination rather than prophylaxis with neuraminidase inhibitors for reducing influenza transmission.[1]

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Cochrane Briefs

Medical Management vs. Surgery for Gastroesophageal Reflux Disease

Clinical Question

For adults, does medical or surgical management of gastroesophageal reflux disease (GERD) result in better outcomes?

Evidence-Based Answer

At one to three years, adults with GERD who were treated with laparoscopic fundoplication had more improvement in overall and GERD-specific quality of life scores and less exposure to acid in the lower esophagus compared with patients who use proton pump inhibitors (PPIs) and histamine H_2 blockers. Participants in the study had characteristics typical of patients with GERD for whom surgery might be considered. (Strength of Recommendation = A, based on consistent, good-quality patient-oriented evidence)

Practice Pointers

Options for GERD management include lifestyle changes such as losing weight, elevating the head of the bed, avoiding late meals or specific foods, and avoiding specific activities that exacerbate symptoms. However, these measures have not been studied in clinical trials. For medical management, PPIs are more effective than H_2 blockers, and both are more effective than placebo. Long-term use of PPIs is often necessary to control symptoms in patients with esophagitis.[1]

In this Cochrane review, the authors searched for randomized and quasirandomized trials comparing treatment of GERD with medical management versus any type of surgical fundoplication. The authors found four studies with a total of 1,232 participants who were followed from one to three years. The studies had a low to medium risk of bias. Although all four studies favored surgery over medical management for the outcome measure of health-related quality of life, data from only two studies could be combined.

The 36-Item Short Form Health Survey (SF-36) is scored from 0 to 100 and measures physical and social functioning, physical and emotional role limitations, mental health, energy, pain, and general health. Compared with medical therapy, the mean difference on scores from the SF-36 was –5.2 (95% confidence interval, –6.8 to –3.6) in favor of surgery. However, a difference of less than 10 may not be clinically significant on this scale. GERD-specific quality of life measures also favored surgery in all four studies. Complication rates in both groups were low. Overall, 4 percent of patients had postoperative complications. In one study, serious adverse events occurred in 21 percent of the surgical group and 14 percent of the medical group. Longer-term comparisons of outcomes were not identified by the authors. Although laparoscopic fundoplication is more costly than medical management in the short and medium term, it may be cost-effective in the longer term.[1]

Because of their safety, the American Gastroenterological Association recommends that PPIs should be the initial therapy, with surgery offered as an alternative if the patient is not responsive to or does not tolerate medical therapy.[2]

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