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Influenza Prevention and Treatment Recommendations

Goal:

- ◆ To increase knowledge of appropriate use of vaccines and medications for treatment and prevention of influenza.

Objectives:

- ◆ List the groups of individuals who are considered a high priority to receive influenza vaccine.
- ◆ Describe the composition of the current influenza vaccine and the process for selection of the particular virus strains for inclusion each year.
- ◆ Describe the results of a cost-effectiveness analysis of influenza vaccine.
- ◆ Discuss the differences in the indications for amantadine, rimanditidine, zanamivir, and oseltamivir.
- ◆ Characterize the patient population that has been involved in the treatment studies of the neuraminidase inhibitor drugs and the magnitude of the treatment benefit that has been shown in completed studies.



Influenza is a highly contagious acute respiratory disease of global importance that has caused epidemics and pandemics of disease for centuries. The influenza A and B viruses cause illness in 10-20% of the population of the United States each year (Couch, 1993).

Influenza epidemics occur in the United States during the winter months and are responsible for nearly 20,000 deaths per year (Anonymous, 1999). In the tropics, influenza can occur all year; in the temperate regions of the Southern Hemisphere, April through September is the most active period. A review of U.S. national data indicate an average of approximately 110,000 hospitalizations per year that are related to influenza (Anonymous, 1999).

Influenza vaccination is the primary method for reducing the impact of this disease. Recent developments for prevention or control of influenza include a new class of antiviral drugs (neuraminidase inhibitors) available this year and an intranasally administered live, attenuated influenza vaccine that may be available next year.

There has been a significant increase in the number of people over the age of 65 getting vaccinated; 33% in 1989 (Anonymous, 1995) to 65.5% in 1997 (Anonymous, 1998). However, there are still many people not receiving the vaccination who should.

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Less than 30% of those younger than 65 years of age who are at high risk for influenza-related complications are vaccinated each year. Increasing vaccination in this group, in particular individuals with diabetes, is a focus of the program for influenza vaccination this year.

Target Groups for Vaccination

The United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommends vaccination for the following groups of people who are at an increased risk for complications from influenza (Anonymous, 1999).

1. Persons aged ≥ 65 years.
2. Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions.
3. Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma.
4. Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immuno-suppression caused by medications).
5. Children and teenagers (aged 6 months to 18 years) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye's syndrome after influenza.
6. Women who will be in the second or third trimester of pregnancy during the influenza season.

There are other groups that should consider getting vaccinated to prevent transmission of the virus to persons at high risk for complications from influenza. These groups include physicians, nurses and other personnel in hospital and outpatient care settings. Employees of nursing homes and assisted living facilities who have contact with patients should also be vaccinated as well as household members of persons in high-risk groups.

Another group to consider for vaccination is HIV infected individuals. Tasker and colleagues, 1999, conducted a randomized, double-blind, placebo controlled trial to determine the efficacy of influenza vaccine in HIV-infected persons. A total of 102 patients were randomized to receive either the influenza vaccine or saline placebo. The mean CD4 count for vaccine recipients was 398 cells/mm³ and 409 cells/mm³ for placebo recipients. Only 5 subjects in the vaccine group and 8 subjects in the placebo group had CD4 counts less than 200 cells/mm³. In this study, 49% of placebo recipients and 29% of vaccine recipients reported respiratory symptoms. Ten placebo recipients, but no vaccine recipients, had laboratory-confirmed symptomatic influenza. No effect on plasma HIV-1 RNA levels or CD4⁺ cell counts was noted. Although the patients in this study were relatively healthy and patients with AIDS were under-represented, the antibody responses of the subjects were similar to those previously reported in patients with AIDS. The conclusion was that the vaccine is highly effective in HIV infected persons and does not seem to be associated with substantial changes in viral load or CD4 cell count. However, in patients who have advanced HIV disease the vaccine might not induce protective antibody titers. The ACIP recommendations state that vaccination will benefit many HIV-infected patients (Anonymous, 1999).

Another group to consider for vaccination is HIV infected individuals.

The vaccine is safe and can be administered to anyone over the age of 6 months who wishes to reduce the chance of becoming ill with influenza. However, there are some people who should not be vaccinated, including anyone known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Persons with acute febrile illness should not be vaccinated until their symptoms have abated.

The vaccine has also been shown to be cost-effective. A cohort study examined the cost-effectiveness of vaccination against influenza in elderly persons living in the community (Nichol, 1994). This study evaluated all persons 65 years

of age or older who were continuously enrolled in Group Health, Inc. (a staff-model health maintenance organization) through the vaccination period and the following influenza seasons: 1990-1991, 1991-1992, and 1992-1993. There were 25,532 persons in the study cohort for 1990-1991; 26,369 for 1991-1992 and 26,626 for 1992-1993. The vaccination rates for the three years were 45%, 58% and 55% respectively. Vaccination was associated with significantly fewer hospitalizations for pneumonia and influenza, and for acute and chronic respiratory conditions in each of the three seasons. In the 1991-92 season, influenza A was epidemic with an excellent match of virus strains and vaccine antigens. In that 1991-92 season the costs of hospitalizations for pneumonia and influenza, all acute and chronic respiratory conditions, and congestive heart failure were significantly lower among vaccine recipients than among unvaccinated persons (reductions of 52%, 47%, and 66% respectively; $p < 0.005$ for all comparisons). Cost savings were also achieved in the other seasons, with an average direct savings per year of \$117 per person vaccinated. The cumulative direct savings in hospitalizations for all acute and chronic respiratory conditions and for congestive heart failure among vaccine recipients over the three years were nearly \$5 million. In addition, vaccination was associated with a significant reduction in all-cause mortality each year (relative risk reduction of 39 to 54 percent).

Types of Vaccines

The currently available influenza vaccine contains three strains (two type A and one type B) that represent the viruses likely to circulate in the United States for the upcoming winter. This year the vaccine for the United States will include A/Beijing/262/95-like (H1N1), A/Sydney/5/97-like (H3N2), and B/Beijing/184/93-like hemagglutinin antigens (Anonymous, 1999). The composition of the vaccine is based on the recommendation of an international network of 110 National Influenza Centres in 83 countries and is coordinated by four WHO Collaborating Centres for Virus Reference and Research in Australia, Japan, the United Kingdom, and the

U.S.A. The recommendations for the vaccine in the Northern Hemisphere are made in mid-February each year and the recommendations for the Southern Hemisphere are made in September.

The optimal time to vaccinate is usually from October through mid-November.

The vaccine is made from purified, egg-grown viruses that have been made noninfectious (inactivated). Whole-virus, split virus, and purified surface-antigen preparations are available. Children aged 6 months to 12 years of age should receive the split virus only. Children over the age of 12 and adults can receive either whole or split virus (Anonymous, 1999). This vaccine is injected intramuscularly.

There is a new type of influenza vaccine that is still undergoing clinical testing. This vaccine is an intranasally administered, cold-adapted, live, attenuated vaccine (LAIV). The viruses in these vaccines replicate in the upper respiratory tract and elicit a specific protective immune response (Anonymous, 1999). The advantages of an intranasal vaccine include the ability to induce a broad mucosal and systemic immune response, ease of administration, and the acceptability of an intranasal route of administration over an injectable route. This vaccine has been tested in both adults and children. In a randomized trial conducted from September 1997 through March 1998 involving 4,561 healthy adults, recipients of the intranasal vaccine experienced fewer severe febrile illnesses (18.8% reduction), fewer lost days of work (17.9% reduction), fewer visits to health care providers (24.8% reduction), and less use of prescription antibiotics and over-the-counter medications compared with placebo (Nichol, 1999).

Another study evaluated the efficacy of the intranasal vaccine in children aged 15-71 months (Belshe, 1998). The trivalent LAIV was 93% effective in preventing culture-positive influenza A (H3N2) and B infections, in reducing otitis media among vaccinated children by 30%, and in reducing the use of antibiotics for otitis media by 35%.

The intranasal vaccine has been shown to be effective, but there have not been any studies that

directly compare the efficacy of the trivalent inactivated (injectable) and the trivalent LAIV (intranasal) vaccine.

Timing of Administration of Influenza Vaccine

Starting each September in the U.S., the vaccine should be offered to persons at high risk when they are seen by health-care providers for routine care or as a result of hospitalization. The optimal time to vaccinate is usually from October through mid-November.

Antiviral Treatment and Prophylaxis of Influenza

Even when immunization programs are implemented, outbreaks of influenza still can occur especially in elderly populations because of a poor response to the vaccine.

Antiviral drugs have been used as an important adjunct to the influenza vaccine for the control and prevention of influenza. The current FDA-approved antiviral drugs for both prevention and treatment of influenza are amantadine and rimantadine. Amantadine and rimantadine are chemically related drugs with specific activity against influenza A but not influenza B viruses. When administered prophylactically to healthy adults or children, both drugs are approximately 70-90% effective in preventing illness from influenza A virus infection, however, the effectiveness of both drugs is substantially lower (30-50%) for elderly populations (Anonymous, 1999).

Amantadine and rimantadine can reduce the severity and shorten the duration of influenza A illness among healthy adults when administered within 48 hours of illness onset. Among children, rimantadine is approved for prophylaxis only, although many experts believe rimantadine is also appropriate for therapy. The potential benefits of these drugs are offset to some extent by the occurrence of central nervous system adverse effects (fewer for rimantadine but it is more expensive) and the emergence and potential spread of drug-resistant strains when either drug is administered to persons who are already infected. To reduce the emergence of drug resistant viruses, treatment of persons who have

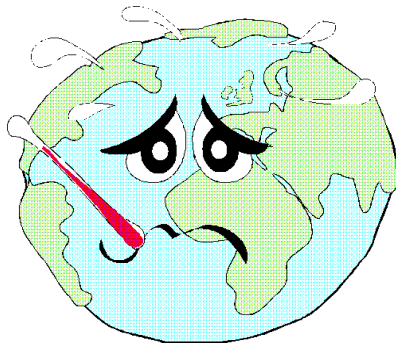
influenza-like illness should be discontinued as soon as clinically warranted; generally after 3-5 days of treatment or 24-48 hours after the disappearance of signs and symptoms (Anonymous, 1999; Hayden, 1997).

Recently, two selective neuraminidase inhibitors, zanamivir and oseltamivir, have been released for the treatment of influenza. This new class of antivirals has activity against both influenza A and B. Zanamivir is the first drug in this class approved by the FDA for the treatment of uncomplicated acute illness due to influenza A and B infections in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. Zanamivir for oral inhalation appears to interrupt infection by preventing viral release from infected cells and by reducing viral penetration of mucus secretions.

Even when immunization programs are implemented, outbreaks of influenza still can occur especially in elderly populations because of a poor response to the vaccine.

In a randomized, double-blind, placebo-controlled trial conducted in the southern hemisphere, 455 patients aged 12 years and older were recruited within 36 hours of the onset of influenza symptoms (Campion, 1998). These patients were randomized to receive inhaled zanamivir 10 mg or placebo twice daily for 5 days. Compared with placebo, zanamivir relieved influenza symptoms a median of 1.5 days earlier in the intent-to-treat population ($p=0.011$), and also in the subset of patients who had laboratory confirmed influenza ($p=0.004$). In the high-risk subgroup (76 total patients), symptoms were alleviated a median of 2.5 days earlier in those treated with zanamivir compared to placebo ($p=0.048$). The high-risk group also experienced a reduction in influenza complications (relative risk 0.29, 95% CI 0.13-0.64) and in associated antibiotic use (relative risk 0.35, 95% CI 0.15-0.81). The risk of complications and antibiotic use in the entire intent to treat population was lower than in the high-risk subgroup and zanamivir did not produce a significant benefit in these outcomes overall.

A prophylaxis trial for 4 weeks of the influenza season also showed that zanamivir reduced the number of laboratory confirmed cases by 67% and the number of cases of influenza with fever by 84% (Monto, 1999). Zanamivir was well tolerated with minimal adverse effects in the



studies. On the evidence available, the U.K.'s National Institute for Clinical Excellence (NICE) concluded there is only moderate

benefit of zanamivir to otherwise healthy individuals and did not recommend it for use during the 1999-2000 flu season by general practitioners in the National Health Service. They note that there is not a great deal of evidence of the impact of the drug on high-risk groups, but there is more research on the way. NICE also advised that vaccination remains the most effective intervention in preventing influenza complications (Yamey, 1999).

Oseltamivir, approved by the U.S. FDA on October 27 1999, is the second drug in the neuraminidase class for the treatment of influenza A and B infections. It has good oral bioavailability and for some patients may be easier to administer than zanamivir, which must be given by oral inhalation. Oseltamivir is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than 2 days. The safety and efficacy have not been established in children less than 18 years of age.

New intranasal vaccines are being developed as an alternative to the injectable form to create an easier method of drug delivery and to eliminate the fear of getting a “shot.”

In support of oseltamivir's new drug application, the sponsor submitted reports of two randomized, double-blind, placebo-controlled

trials in adults (age 18 to 65 years) with uncomplicated influenza. These trials enrolled a total of 1358 individuals; 849 were diagnosed with confirmed influenza. In these trials it was demonstrated that treatment with oseltamivir in the influenza infected adults resulted in a 1.3 day reduction in the median time until symptom improvement (Jolson, 1999). The most frequently reported adverse effects of oseltamivir were nausea, vomiting, bronchitis, trouble sleeping and dizziness. Rates of withdrawal due to adverse events were “infrequent.” Efficacy of oseltamivir in populations with chronic cardiac disease or respiratory disease has not been established. The recommended dose in the FDA approved product labeling of oseltamivir is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms.

Conclusion

The influenza virus can be deadly if the right precautions are not taken. Vaccination is highly recommended for all people over the age of 65 years, all people with chronic medical conditions, and all health care workers. But anyone who wishes to reduce the chance of becoming ill can be vaccinated. New intranasal vaccines are being developed as an alternative to the injectable form to create an easier method of drug delivery and to eliminate the fear of getting a “shot.”

Amantadine and rimantadine are available as adjunct for treatment and prevention of influenza as well. They do not replace the need for vaccination, however. There are two promising new drugs for the treatment of influenza, zanamivir and oseltamivir. It is too early to tell what role these new drugs should play in the management of the influenza virus. Antiviral medications may be considered for prophylaxis of influenza in persons: at high risk who are vaccinated after influenza activity has begun, who are providing care to those at high risk, who are immunodeficient, and who should not receive the vaccine. Antiviral medications may be considered for treatment of influenza for patients identified within 36 to 48 hours of onset of illness to reduce the severity and duration of illness. More data are needed to clarify the circumstances for optimal

use of antiviral medications. Until then, get vaccinated!

Search Strategy

The *IDIS* database offers many options for retrieval of primary literature to evaluate the use of the influenza vaccine for prevention of influenza. Search terms entered in the global field give a broad overview of the number of articles based on the subject of interest. Entering *influenza* in the Global field retrieves 1,746 articles within the *IDIS* database. A specific search using *IDIS* classification numbers would be more useful. Click on the Thesaurus tab, type *influenza*, and press <ENTER> to find the *IDIS* valid term and code number. This generates a list of valid terms and code numbers for influenza the disease (487.) and the influenza vaccine (80120006). On the main search page, type (or copy and paste from the thesaurus) these numbers in the Drug and Disease fields (remember to include the decimal point in the disease term), use the Boolean operator AND, and press <ENTER>. This will search the database for all articles relating to influenza and the influenza vaccine. This yields 616 articles. You can also look for articles that pertain to drug therapy for influenza, such as amantadine, rimantadine, zanamivir, or oseltamivir (also known as GS-4104). Just click on the Thesaurus tab and type the drug you wish to search. For example, when *zanamivir* is typed into the Thesaurus, the number 8180096 appears. This number can be typed in the Drug field on the main search page. This yields 27 search results for zanamivir. Another way to limit the search is to use descriptors. On the main search page, click the Look Up icon and scroll through the descriptor list, then select a term by checking the box beside the term and click on OK. To search for the intranasal influenza vaccine, use *126 ADM Nose* in the Descriptor field along with the influenza drug and disease numbers found earlier. This will yield 30 search results for the intranasal influenza vaccine. To find articles dealing only with the injectable vaccine, use the *117 ADM PARENT INTRAMUSCULAR* descriptor in combination with the influenza drug and disease terms. This yields 76 articles. You can further limit the search

to specific types of studies, pharmacokinetics, side effects, etc. by using different descriptors. To find articles about the cost-effectiveness of the influenza vaccine, type the drug term found above in to the correct field, select 129 ECON DRUG ECONOMICS OR 131 ECON COST EFFECTIVENESS from the list of descriptors. To include all of the economic study designs you can just type *ECON* in the descriptor field. This will retrieve all articles in *IDIS* that pertain to economics or cost-effectiveness of the influenza vaccine.

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Nichol KL, Margolis KL, Wuorenma J, and Von Sternberg T. The Efficacy and Cost Effectiveness of Vaccination Against Influenza Among Elderly Persons Living in the Community. *N Engl J Med*. 1994;331:778-784. (IDIS Article Number 335148)

Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of Live, Attenuated Intranasal Influenza Virus Vaccine in Healthy, Working Adults. *JAMA*. 1999;282:137-144. (IDIS Article Number 429039)

Tasker SA, Treanor JJ, Paxton WB, Wallace MR. Efficacy of Influenza Vaccination in HIV-Infected Persons: a Randomized, Double-blind, Placebo-controlled trial. *Ann Intern Med*. 1999;131:430-433. (IDIS Article Number 432664)

Yamey G. Dobson Backed NICE Ruling on Flu Drug. *BMJ*. 1999;319:1024.

RENEWAL

REMINDER: Renewal materials for the 2000 IDIS database subscription were mailed in early September and again in November. We ask that you respond as soon as possible. **Your current subscription will expire after the December 1999 update.**

To avoid interruption of service, your renewal must be received by January 12, 2000. In the event you misplace or fail to receive a renewal form, please contact our office as soon as possible. Thank you for your prompt attention to your 2000 subscription renewal.



Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACEP program number is 020-000-99-901-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.



To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation, and return with processing fee of U.S.\$5.00 to Division of Drug Information Service. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists completing this program by December 1, 2000 can receive credit.

Assessment Questions

Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

1. Complete the answer sheet.
2. Print or type your name, address, social security number and pharmacy license number(s) in the space provided on the CE registration form.
3. Complete the program evaluation.

Mail processing fee of U.S.\$5.00 (payable to the College of Pharmacy), your completed answer sheet, registration form and evaluation to:

**Division of Drug Information Service
ATTN: Donna Brus
The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000**

Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified, and no credit will be recorded. Allow four weeks for processing.

- 1. Which of the following is the most common method of preventing influenza?**
 - A) Amantadine
 - B) Influenza vaccine
 - C) Zanamivir
 - D) Rimantadine
 - E) Oseltamivir
- 2. According to the Advisory Committee on Immunization Practices (ACIP), which of the following is a target group for influenza vaccination?**
 - A) Persons aged ≥ 65 years
 - B) Residents of nursing homes or other chronic-care facilities
 - C) Adults and children who have chronic disorders of the pulmonary or cardiovascular system
 - D) Women who will be in the second or third trimester of pregnancy during the influenza season
 - E) All of the above
- 3. Who should NOT be vaccinated?**
 - A) People with an anaphylactic reaction to eggs
 - B) Household members of persons in high-risk groups
 - C) People with acute, febrile illness after symptoms have abated
 - D) Children less than 10 years of age
 - E) Health care workers
- 4. Which of the following is NOT an advantage of the intranasal, cold-adapted, live, attenuated vaccine?**
 - A) It contains inactivated viruses
 - B) It can induce a broad mucosal immune response
 - C) Its ease of administration
 - D) It is effective in children
 - E) It may be a more acceptable route of administration than the injectable vaccine
- 5. The optimal time to vaccinate in the U.S. for influenza is in the spring.**
 - A) True
 - B) False
- 6. Antiviral drugs have been used as a substitute to the influenza vaccine for the control and prevention of influenza.**
 - A) True
 - B) False
- 7. Which one of the following have been approved by the FDA for the prevention and treatment of influenza?**
 - A) Amantadine and rimantadine
 - B) Rimantadine and zanamivir
 - C) Zanamivir and Oseltamivir
 - D) All are correct
 - E) None
- 8. In order to reduce the emergence of drug resistant viruses, the treatment of persons who have influenza should be**
 - A) Discontinued as soon as clinically warranted
 - B) Continued until the end of influenza season
 - C) Discontinued 24 to 48 hours after disappearance of signs and symptoms of influenza
 - D) A and B
 - E) A and C
- 9. Which one of the following is CORRECT regarding zanamivir?**
 - A) The potential benefits of zanamivir are usually offset by the occurrence of CNS adverse reactions.
 - B) Zanamivir is in the same pharmacological class as amantadine and rimantadine.
 - C) Zanamivir has a good oral bioavailability and easier to administer than oseltamivir
 - D) Zanamivir is effective in the treatment of influenza A and B infections
 - E) None of them are correct
- 10. Which one of the following is NOT true?**
 - A) Even when immunization programs are implemented, outbreak of influenza still occur.
 - B) Zanamivir for inhalation appears to interrupt infection by preventing viral release and reducing viral penetration of mucus secretions.
 - C) Amantadine and rimantadine are more effective in preventing illness from influenza A virus infection in elderly than in adults and children.
 - D) Oseltamivir has shown to reduce the duration of illness when administered within 36 hours of onset of influenza symptoms
 - E) All are true

ANSWER SHEET

Circle the most appropriate answer

- | | | | | | | | | | | | |
|----|---|---|---|---|---|-----|---|---|---|---|---|
| 1. | a | b | c | d | e | 6. | a | b | | | |
| 2. | a | b | c | d | e | 7. | a | b | c | d | e |
| 3. | a | b | c | d | e | 8. | a | b | c | d | e |
| 4. | a | b | c | d | e | 9. | a | b | c | d | e |
| 5. | a | b | | | | 10. | a | b | c | d | e |

CE REGISTRATION

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Signature Date

PROGRAM EVALUATION

	Excellent				Poor
Overall Quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of Content	5	4	3	2	1
	Agree				Disagree
Important to Pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

Pharmacoeconomic Descriptors

Healthcare practitioners must consider cost in addition to efficacy and safety when selecting therapy options. The *IDIS* database responded to this need in November 1993, by adding six economic outcome descriptors. The purpose of this article is to help clarify the *IDIS* definitions for these descriptors.

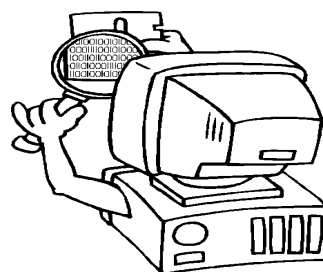
The definitions of the descriptors are located in the tab section of the *IDIS* main search screen. Click on the tab descriptors to access the definitions. Typing *cost* econ** in the field, you retrieve six economics outcome descriptor terms.

- 129 ECON DRUG ECONOMICS
- 130 ECON COST BENEFIT
- 131 ECON COST EFFECTIVENESS
- 132 ECON COST MINIMIZATION
- 133 ECON COST OF ILLNESS
- 134 ECON COST UTILITY

The economics descriptor terms begin with "ECON" followed by the study type. The pharmacoeconomics definitions are based on the criteria by Luce & Elixhauser and consider ***intervention cost and consequence measurements***. Intervention costs are generally measured in monetary values, while it is the measurement of the *consequences* that differentiates the study type.

The descriptor, **ECON DRUG ECONOMICS**, by definition is used for articles that identify, assess, compare or analyze the cost of drug therapy and its implications for the individual, institutions and society. This descriptor is the general term for the economics class and is used if the resources consumed and consequences are not included in the article. Examples of articles that use this descriptor are drug budget costs for a hospital or the amount saved by pharmacists' involvement in therapeutic drug monitoring.

ECON COST BENEFIT studies measure both the ***resources consumed*** and the ***outcome consequences in monetary values***. An example of this article type is, "Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings" (*IDIS* article number 428170). The resources consumed include the cost of palivizumab and its administration. The prevention savings include the risk reduction of hospitalization and disease treatment costs. The drug intervention and the prevention savings are both measured in monetary terms. Emphasis is on the outcome benefit in costs saved.



ECON COST EFFECTIVENESS studies differ from cost benefit in the outcome measures. Cost effectiveness studies focus on ***health benefits achieved, not cost savings***. The consequences of the drug therapy are measured in cost per cases treated, or cost per lives saved or other non-monetary outcomes. An example of this article type is "Supplemental calcium for the prevention of hip fracture: potential health-economic benefits" (*IDIS* article number 432238). The results of the study show calcium cost per hip fracture cases prevented due to calcium supplementation.

ECON COST MINIMIZATION studies ***compare alternative drug therapies*** with equal clinical efficacy to determine the ***lowest cost*** for disease treatment. These studies are helpful in comparing new drugs or drugs with new approved uses to the standard drug therapy for a disease. An example is "Azithromycin

vs. erythromycin for community-acquired pneumonia: a cost-minimization analysis” (*IDIS* article number 429565).

ECON COST OF ILLNESS descriptor encompasses the full economic burden of the illness. It measures **direct costs** such as drug therapy or hospitalization. It also includes the **indirect costs** associated with the disease, such as cost of productivity losses. It may also compare the costs based on the patient’s severity of illness. An example is “Economic consideration in Alzheimer’s disease” (*IDIS* article number 416895).

ECON COST UTILITY studies look at the cost of therapy and measure the health benefits achieved based on **quality of life**. An example of this type of study is “Hepatitis C: an evaluation of extended treatment with interferon” (*IDIS* article number 432742). The results measure interferon cost per

quality-adjusted life-year gained. These results are sensitive to the assumptions made about quality of life based on established scales.

Pharmacoeconomics is an important part of drug therapy decisions for healthcare professionals. The *IDIS* database has responded to the challenge to provide the necessary search terms to facilitate retrieval of relevant economic studies for drug therapy decisions.

Reference: Luce BR, Elixhauser A. Standard for socioeconomic evaluation of health care products and services. Berlin, Germany: Springer-Verlag;1990:95



Mary Ann Cull, R.Ph.

Y2K COMPLIANCY

Relax - *IDIS* System/CD-ROM is Year 2000 compliant. The publication year is the only date field in the database and is currently in four-digit format. There is no code in the retrieval software that is affected by the system date. Please contact us if you need additional information.



FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Dalfopristin and Quinupristin (1S)** <i>Synercid</i>	Rhone-Poulenc Rorer (Sept. 21)	DALFOPRISTIN 8122924 QUINUPRISTIN 8122932 (94 citations)	Treatment of infections associated with vancomycin-resistant <i>Enterococcus faecium</i> and for complicated skin and skin structure infections caused by methicillin-susceptible <i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i>	Infection, Streptococcus D 041.04 Infection, <i>Staph Aureus</i> 041.11 Infection, Streptococcus A 041.01
Dofetilide (1S) <i>Tikosyn</i>	Pfizer (Oct. 1)	DOFETILIDE 24040067 (39 citations)	For the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter (AF/AFI) in patients with atrial fibrillation/atrial flutter of great than one week duration who have been converted to normal sinus rhythm	Fibrillation, Atrial 427.3
Entacapone (1S) <i>Comtan</i>	Orion Corp (Oct 19)	ENTACAPONE 44100072 (28 citations)	Use as an adjunct to levodopa/carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (so-called "fluctuating" patients)	Parkinson's Disease 332.
Epirubicin (1P***, V****) <i>Ellence</i>	Pharmacia & Upjohn Co. (Sept. 15)	EPIRUBICIN 10030005 (394 citations)	For use as a component of adjuvant therapy following resection of early stage breast cancer that has spread to the lymph nodes under the arm	NEOP, MGN-Female Breast 174.
Exemestane (1S) <i>Aromasin</i>	Pharmacia & Upjohn Co. (Oct. 21)	EXEMESTANE 10120110 (9 CITATIONS)	For the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.	NEOP, MGN-Female Breast 174. Disorder, Menopause/Post NEC 627.
Oseltamivir Phosphate (1P) <i>Tamiflu</i>	Roche (Oct. 27)	OSELTAMIVIR 8180099 (6 citations)	For the treatment of uncomplicated influenza in adults whose flu symptoms have not lasted more than two days	Influenza 487.

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	Valid IDIS Disease Term Modified ICD-9- CM Number
Pemiroloast Potassium (1P) <i>Alamast</i>	Santen (Sept. 24)	PEMIROLAST 4000032 (5 citations)	Prevention of itchy eyes due to allergic conjunctivitis	Conjunctivitis, Acute 372.0 Conjunctivitis, Chronic 372.1
Rabeprazole Sodium (1S) <i>Aciphex</i>	Eiasi (Aug. 19)	RABEPRAZOLE 56400029 (11 citations)	Proton pump inhibitor for healing or maintenance therapy of erosive or ulcerative gastroesophageal reflux disease (GERD); healing of duodenal ulcer and treatment of pathological hypersecretory conditions, including Zollinger Ellison Syndrome	Esophagitis 530.1 Abnormality, Gastrin Secret 251.5 Ulcer, Duodenal 532.
Rapacuronium Bromide (1S) <i>Raplon</i>	Organon (Aug. 18)	RAPACURONIUM 12200033 (19 citations)	For adjunctive use with general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgical procedures	Anesthesia/ Paresthesia 782.0 Intubation and Irrigation 96.
Sirolimus (1P) <i>Rapamune</i>	Wyeth Ayerst (Sept. 15)	SIROLIMUS 92000235 (77 citations)	For use in combination with cyclosporine and corticosteroids for prevention of organic rejection in patients receiving renal transplants	Complication, Organ Transpl 996.8 Prophylaxis NEC V07. Transplant, Kidney 55.6
Technetium Tc 99m Depreotide (1P) <i>NeoTect</i>	Diatide (Aug. 3)	TC 99M DEPREOTIDE 78040257 (2 citations)	Imaging agent for use in detecting malignant lung tumors	NEOP, MGN- Bronchus/Lung 162. Radioisotope Scan, Pulmonary 92.15
Temozolomide (1P,V) <i>Temodar</i>	Schering- Plough (Aug. 11)	TEMOZOLOMIDE 10040037 (13 citations)	Treatment of adult patients with refractory anaplastic astrocytoma, ie., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine	NEOP, MGN-Brain 191.
Zaleplon (1S) <i>Sonata</i>	Wyeth Ayerst (Aug. 13)	ZALEPLON 28240856 (11 citations)	For the short-term treatment of insomnia	Disturbance, Sleep 780.5

* Through November 1999 Update. Complete bibliographic citations will be provided upon request.

** (1S) New Molecular Entity given standard review by FDA

*** (1P) New Molecular Entity given priority review by FDA

**** (V) Orphan Drug

New Drug Selected Bibliography



KEY
REFERENCES

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA from August through October 1999.

IDIS SYSTEM/CD-ROM was searched to retrieve key articles relevant to the new drugs and their approved uses.

Dalfopristin/Quinupristin

Linden PK, Pasculle AW, McDevitt D et al. Effect of quinupristin/dalfopristin on the outcome of vancomycin-resistant *Enterococcus faecium* bacteraemia: comparison with a control cohort. *J Antimicrob Chemother* 1997;39:145-

151. (*IDIS Article Number 388048*). **A study in which investigators compared 20 patients with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia treated with dalfopristin/quinupristin, intravenously 7.5 mg/kg every 8 hours, with a historical cohort of 42 patients with VREF bacteremia treated with other antimicrobial agents.**

Cupo-Abbott J, Holtom P, Rho JP. Quinupristin/Dalfopristin: an investigational streptogramin antibiotic for the treatment of multidrug-resistant gram-positive infections. *Formulary* 1998;33:841-857. (*IDIS Article Number 414950*). **This article is a recent review of quinupristin/dalfopristin and its use in the treatment of VREF and methicillin-resistant *Staphylococcal aureus* infections.**

Griswold MW, Lomaestro BM, Briceland LL. Quinupristin-dalfopristin (RP 59500): An injectable streptogramin combination. *Am J Health-Syst Pharm* 1996;53:2045-2053. (*IDIS Article Number 371641*). **A comprehensive review of the combination drug: quinupristin/dalfopristin.**

Dofetilide

Norgaard BL, Wachtell K, Christensen PD et al. Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled trial. *Am Heart J* 1999;137:1062-1069. (*IDIS Article Number 429649*). **Investigators conducted a multi-center, randomized, double blind, placebo controlled trail to evaluate the efficacy and safety of intravenous dofetilide, 8 micrograms/kg of body weight over 30 minutes, in 96 patients with a sustained rhythm of atrial fibrillation or atrial flutter, duration from one hour to six months, with hemodynamic stability and without symptoms of uncontrolled heart failure.**

Falk RH, Pollak A, Singh SN et al. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of

sustained atrial fibrillation or flutter. *J Am Coll Cardiol* 1997;29:385-390. (*IDIS Article Number 380993*). **In a double blind, randomized, placebo controlled multi-center study, investigators assessed the efficacy and safety of a single bolus of intravenous dofetilide, 4 or 8 micrograms/kg of body weight, in 91 patients with sustained atrial fibrillation or flutter of two weeks to six months duration.**

Entacapone

Rinne UK, Larsen JP, Siden A et al. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology* 1998;51:1309-1314. (*IDIS Article Number 417611*). **In a six month randomized, double blind multi-center trial, investigators studied the effect and safety of 200mg entacapone or placebo given concomitantly with each daily scheduled dose of levodopa in 171 parkinsonian patients with wearing-off-type motor fluctuations.**

Kiebertz K, Shoulson I, Fahn S et al. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients: Parkinson Study Group. *Ann Neurol* 1997;42:747-755. (*IDIS Article Number 397305*). **To test the hypothesis that by slowing elimination of levodopa, entacapone would benefit Parkinson's disease patients affected by wearing off phenomenon, investigators conducted a 24 week, double blind, multi-center trial with 205 parkinsonian patients randomized to receive either entacapone 200mg or matching placebo with each dose of levodopa.**

Epirubicin

Levine MN, Bramwell VH Pritchard KI et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol* 1998;16:2651-2658. (*IDIS Article Number 410689*). **Investigators conducted a randomized, open-label multi-center study to determine the relative efficacy of a six-month intensive cyclophosphamide, epirubicin, and fluorouracil adjuvant chemotherapy regimen compared with a standard cyclophosphamide, methotrexate and fluorouracil regimen in 716 premenopausal women with node-positive breast cancer. (One of two pivotal studies on which FDA approval was based.)**

Coombes RC, Bliss JM, Wils J et al Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. *J Clin Oncol* 1996;14:35-45. (*IDIS*

Article Number 358666). *A randomized multi-center study was conducted to investigate whether replacing methotrexate in the cyclophosphamide, methotrexate, and fluorouracil regimen would improve the relapse-free and overall survival rates in 759 premenopausal patients with axillary node-positive operable breast cancer.*

Oseltamivir

Hayden FG, Treanor JJ, Fritz RS et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;282:1240-1246. (IDIS Article Number 434353). *Investigators conducted two randomized, double blind, placebo controlled trials to determine the safety, tolerability, and antiviral activity of oseltamivir for the prevention and early treatment of influenza in 117 experimentally infected healthy volunteers.*

Rabeprazole

Cloud ML, Enas N, Humphries TJ et al. Rabeprazole in treatment of acid peptic diseases. Results of three placebo-controlled dose-response clinical trials in duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD). *Dig Dis Sci* 1009;73:993-1000. (IDIS Article Number 406275). *A report of three placebo-controlled, double-blind, randomized multi-center studies in which investigators compared the efficacy of rabeprazole, 10 to 40mg once daily, and placebo in 297 patients with duodenal ulcer, gastric ulcer, or GERD.*

Stack WA, Knifton A, Thirlwell D et al. Safety and efficacy of rabeprazole in combination with four antibiotic regimens for the eradication of *Helicobacter pylori* in patients with chronic gastritis with or without peptic ulceration. *Am J Gastroenterol* 1998;93:1909-1913. (IDIS Article Number 414937). *Investigators conducted a randomized double-blind study to evaluate the efficacy and safety of rabeprazole 20mg in combination with four different seven day antibiotic regimens in 75 H. pylori infected patients.*

Rapacuronium

Schiere S, van den Broek L, Proost JH et al. Comparison of vecuronium with Org 9487 and their interaction. *Can J Anaesth* 1997;44:1138-1143. (IDIS Article Number 397250). *In a randomized controlled study investigators compared the onset of action of equipotent doses of Org 9487 (rapacuronium) and vecuronium and investigated their mutual interaction when given in succession to 60 anesthetized patients.*

Wierda JM van den Broek L Proost JH et al. Time course of action and endotracheal intubating conditions of Org 9487, a new short-acting steroidal muscle relaxant; a comparison with succinylcholine. *Anesth Analg* 1993;77:579-584. (IDIS Article Number 319831). *Investigators conducted a randomized study in 45 anesthetized patients to compare the endotracheal*

intubating conditions and onset of action of succinylcholine and Org 9487 (rapacuronium) with or without reversal with neostigmine, administered two minutes after injection of Org 9487.

Sirolimus

Kahan BD, Podbielski J, Napoli KL et al. Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. *Transplantation* 1998;66:1040-1046. (IDIS Article Number 416821). *Investigators conducted an open label phase I/II dose-escalation study in forty mismatched living-donor renal transplant recipients sequentially assigned to receive escalating initial doses of sirolimus (0.5-7.0 mg/m²/day) in addition to courses of prednisone and a concentration-controlled regimen of cyclosporine and compared these results to a historical cohort of 65 similar patients treated with the same regimen of cyclosporine and prednisone.*

Technetium Tc 99m Depreotide

Blum JE, Handmaker H, Rinne NA. The utility of a somatostatin-type receptor binding peptide radiopharmaceutical (P829) in the evaluation of solitary pulmonary nodules. *Chest* 1999;115:224-232. (IDIS Article Number 424429). *Investigators conducted this study to determine the ability of P829 (Technetium Tc 99m Depreotide) scintigraphy to noninvasively differentiate malignant and nonmalignant solitary pulmonary nodules in thirty patients with indeterminate solitary pulmonary nodules and used transthoracic needle biopsy to confirm malignancy detected by abnormal scans.*

Zaleplon

Greenblatt DJ, Harmatz JS, von Moltke LL et al. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin Pharmacol Ther* 1998;64:553-561. (IDIS Article Number 416031). *In a double blind, five condition crossover study investigators evaluated the pharmacokinetics, pharmacodynamics, and kinetic-dynamic relationships of single oral doses of 10-20mg doses of zaleplon and compared these properties to zolpidem.*

Additional information on these newly approved drugs will be available in the Summary Basis of Approval (an official United States Food and Drug Administration [FDA] document) that is compiled for each new drug being reviewed. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. Following the FDA approval of a new drug, these documents are requested from the FDA and are then indexed and included as part of the IDIS database. Use descriptor 155 SUMMARY BASIS OF APPROVAL in combination with the valid drug term to retrieve these documents from the database.



Ruth Calloway, R.Ph., M.S.



STAFF
PROFILE

Duane Dunkerson joined the DDIS staff as a Project Research Assistant in May of 1999. He earned an MA in applied linguistics from University of Northern Iowa in 1999. Duane and his wife Joseli live in Coralville, Iowa. She is completing a Ph.D. in dental public health. Duane serves as the liaison for the Australian component of the Transnational Alliance (TNA). The TNA is exploring international

cooperation to further Web access to drug information. He is compiling Iowa Drug Information Network survey and interview data from 22 preceptor sites in Iowa. These interviews were done on-site by Duane.

In his free time, Duane plays chess, watches the moon, does research in microbiology and is a "wait-till-next-year" Cub fan.

Duane Dunkerson

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