Therapeutic Class Overview
Antivirals: Influenza

Therapeutic Class

- **Overview/Summary:** Influenza epidemics are a major cause of respiratory illness in the United States.[1] The most effective way to minimize the negative impact of influenza is through prophylaxis, by administration of the influenza vaccine.[1] Guidance for the 2014-2015 season follows the recommendations from the 2013-2014 influenza season. Interim guidance continues to recommend annual influenza vaccination for all persons six months of age and older in the United States.[2] It is specifically recommended annually for older persons (≥65 years of age), young children, pregnant women and individuals considered high risk, including immunocompromised persons and those with comorbidities such as chronic pulmonary, cardiovascular and chronic metabolic diseases, or any disorder interfering with respiratory function. The general population should be vaccinated once the above populations have had the opportunity to be vaccinated. The use of chemotherapeutic agents for the prophylaxis and treatment of influenza is an important adjunct for disease control during outbreaks among unvaccinated individuals, or for individuals at risk for whom the vaccine is contraindicated or ineffective.[1]

  The neuraminidase inhibitors and the adamantanes are the two classes of drugs available for the prophylaxis and treatment of influenza. The neuraminidase inhibitors, oseltamivir and zanamivir are Food and Drug Administration (FDA)-approved for the treatment and prophylaxis of influenza A and B.[3,4] Neuraminidase inhibitors block viral release during the replication cycles of influenza A and B. Through inhibition of neuraminidase, the new virions are tethered to the cellular membrane glycoproteins of their parent cells and cannot spread to other cells.[5,6] Oseltamivir and zanamivir should be administered as early as possible and are indicated only for use during the first two days of symptomatic illness.[3,4,7] When used for the treatment of influenza, oseltamivir is FDA-approved for use in persons two weeks of age and older, and zanamivir may be used in persons seven years of age and older. As influenza prophylaxis oseltamivir is approved for use in persons one year of age and older, while zanamivir is approved for prophylaxis in persons five years of age and older. It is important to note that oseltamivir and zanamivir are not substitutes for early vaccination on an annual basis as recommended above.[3,4] Zanamivir should not be used for the prophylaxis or treatment of influenza in individuals with underlying airway disease.[4] The adamantanes, amantadine and rimantadine, prevent viral replication by blocking the viral M2 protein ion channel, which prevents fusion of the virus and host-cell membranes.[8,9] Amantadine and rimantadine, are active only against influenza A.[1] Both amantadine and rimantadine are approved for prophylaxis and treatment of influenza A.[8,9] Due to a marked increase in resistant isolates, the Advisory Committee on Immunization Practices recommends that adamantanes not be used in the United States for the treatment of influenza, except in selected circumstances.[1]

Table 1. Current Medications Available in the Class[3,4,8,9,10,11]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Amantadine (Symmetrel*)	Prophylaxis against signs and symptoms of influenza A virus infection, treatment of drug-induced extrapyramidal reactions, treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism and symptomatic parkinsonism and treatment of uncomplicated respiratory tract illness caused by influenza A virus	Capsule: 100 mg Oral syrup: 50 mg/5 mL Tablet: 100 mg	✔
Oseltamivir (Tamiflu®)	Prophylaxis of influenza in patients one year of age and older and treatment of acute, uncomplicated illness due to influenza infection in patients two	Capsule: 30 mg 45 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	weeks of age and older who have been symptomatic for no more than two days	75 mg Powder for oral suspension: 6 mg/mL	
Rimantadine (Flumadine®*)	Prophylaxis against signs and symptoms of influenza A virus infection and treatment of illness caused by various strains of influenza A virus in adults	Tablet: 100 mg	✔
Zanamivir (Relenza®)	Prophylaxis of influenza in patients five years of age and older and treatment of uncomplicated acute illness due to influenza A and B in patients seven years of age and older who have been symptomatic for no more than two days	Blister for oral inhalation: 5 mg/ actuation	-

*Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- Oseltamivir and zanamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated reduced laboratory-confirmed influenza, decreased illness, fever duration, secondary complications, as well as a reduction in household contacts with influenza infection.[12-35] Head-to-head trials directly comparing the agents are limited.
- Kawai and colleagues compared oseltamivir to zanamivir for the treatment of both influenza A and B. Results demonstrated significantly shorter fever duration in patients with influenza B who were treated with zanamivir, compared to those treated with oseltamivir.[32]
- Tuna et al found that for overall efficacy, oseltamivir and zanamivir had no significant difference, but temperature normalization was significantly faster in the zanamivir group (P=0.0157).[33]
- Clinical trials have demonstrated that amantadine and rimantadine are also effective in both the prophylaxis and treatment of influenza A; however, these agents are not routinely recommended for the treatment of influenza.[31,35,37-47]
- With regard to Parkinson's disease, data from one clinical trial included in a meta-analysis demonstrated that patients receiving amantadine as monotherapy or adjuvant therapy for idiopathic Parkinson's disease achieved greater benefits in Parkinsonian symptoms severity scale scores and activity impairment scale scores compared to placebo. Furthermore, for the treatment of drug-induced extrapyramidal reactions, amantadine has demonstrated efficacy in reducing dyskinesia frequency and severity, as well as motor complications in patients with Parkinson's disease.[48-55]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to the Centers for Disease Control and Prevention, the most effective way to minimize the negative impact of influenza is through prophylaxis, by administration of the influenza vaccine.[1]
  - An annual influenza vaccination is recommended for all persons six months of age and older in the United States.[2]
  - Antiviral treatment is recommended as soon as possible for:
    - Patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.[56-60]
    - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions.[56-60]
  - Persons at higher risk for influenza complications recommended for antiviral treatment include:
    - Children less than two years of age.
    - Adults aged ≥65 years.

        - Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury).
        - Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection.
        - Women who are pregnant or postpartum (within two weeks after delivery).
        - Persons aged <19 years who are receiving long-term aspirin therapy.
        - American Indians/Alaska Natives.
        - Persons who are morbidly obese (i.e., body-mass index ≥40).
        - Residents of nursing homes and other chronic-care facilities.[56-60]
    - Oseltamivir and zanamivir are active against both influenza A and B. Rimantadine and amantadine are only active against influenza A.[56-60]
    - Amantadine and rimantadine should not be used due to the high levels of resistance to these drugs.[56-60]
- Other Key Facts:
    - Amantadine and rimantadine are available generically; however, they should not be used for the treatment of influenza, except in selected circumstances.[56-60]

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Therapeutic Class Review
Antivirals: Influenza

Overview/Summary

Influenza epidemics occur nearly every year, usually during the winter months, in temperate climates, making this disease a major cause of respiratory illness in the United States (U.S.).[1] The majority of complications, hospitalizations and deaths from influenza occur in persons over 65 years of age, young children, and persons of any age with certain underlying health conditions.[1] According to the Centers for Disease Control and Prevention (CDC), the most effective way to minimize the negative impact of influenza is through prophylaxis, by administration of the influenza vaccine.[1] Guidance for the 2014-2015 season follows the recommendations from the 2013-2014 influenza season. Interim guidance from the Advisory Committee on Immunization Practices continues to recommend annual influenza vaccination for all persons six months of age and older in the U.S.[2] It is specifically recommended annually for older persons (≥65 years of age), young children, pregnant women and individuals considered high risk, including immunocompromised persons and those with comorbidities such as chronic pulmonary, cardiovascular and chronic metabolic diseases, or any disorder interfering with respiratory function. The CDC recommends vaccination of the general population once the patient populations previously outlined have had the opportunity to be vaccinated, which may be dictated by that year's vaccine supply. The use of chemotherapeutic agents for the prophylaxis and treatment of influenza is an important adjunct for disease control during outbreaks among unvaccinated individuals, or for individuals at risk for whom the vaccine is contraindicated or ineffective.[1]

The neuraminidase inhibitors and the adamantanes are the two classes of drugs available for the prophylaxis and treatment of influenza. The neuraminidase inhibitors, oseltamivir and zanamivir are Food and Drug Administration (FDA)-approved for the treatment and prophylaxis of influenza A and B.[3,4] Neuraminidase inhibitors work by blocking viral release mechanisms during the replication cycles of influenza A and B. Neuraminidase is necessary for release of daughter virions from infected cells. Without the action of neuraminidase, the new virions are tethered to the cellular membrane glycoproteins of their parent cells and cannot spread to other cells.[5,6] Oseltamivir and zanamivir must be administered as early as possible and are indicated only for use during the first two days of symptomatic illness.[3,4,7] When used for the treatment of influenza, oseltamivir is FDA-approved for use in persons two weeks of age and older, and zanamivir may be used in persons seven years of age and older. As influenza prophylaxis oseltamivir is approved for use in persons one year of age and older, while zanamivir is approved for prophylaxis in persons five years of age and older. Oseltamivir and zanamivir are not substitutes for early vaccination on an annual basis as recommended by the CDC. [3,4] Zanamivir should not be used for the prophylaxis or treatment of influenza in individuals with underlying airway disease.[4] The neuraminidase inhibitors have been used off-label for the treatment and prophylaxis of avian influenza and Novel influenza A, H1N1.[8]

The adamantanes, amantadine and rimantadine, prevent viral replication by blocking the viral M2 protein ion channel, which prevents fusion of the virus and host-cell membranes.[9,10] Amantadine and rimantadine, are active only against influenza A, not influenza B.[1] Both amantadine and rimantadine are approved for prophylaxis and treatment of influenza A.[9,10] Due to a marked increase in resistant isolates, the Advisory Committee on Immunization Practices recommends that adamantanes not be used in the U.S. for the treatment of influenza, except in selected circumstances.[1] Amantadine was also found to have therapeutic value in relieving symptoms of Parkinson's disease in some patients.[11] It is currently approved for the treatment of idiopathic Parkinson's disease, parkinsonism and drug-induced extrapyramidal reactions.[12] Its mechanism of action as a central nervous system agent is not established, but it is thought to block the reuptake of dopamine in presynaptic neurons and also to cause direct stimulation of postsynaptic receptors.[13] It also blocks N-methyl-D-aspartate receptors, which may explain its role in controlling dyskinesia.[14] Amantadine is less effective than levodopa in the treatment of Parkinson's disease, but that it has fewer associated extrapyramidal reactions than anticholinergic antiparkinson drugs.[13]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Amantadine (Symmetrel*)	Adamantane	✔
Oseltamivir (Tamiflu®)	Neuraminidase inhibitor	-
Rimantadine (Flumadine®*)	Adamantane	✔
Zanamivir (Relenza®)	Neuraminidase inhibitor	-

*Generic available in at least one dosage form and/or strength.

Antiviral resistance profiles for currently circulating influenza A and B viruses are listed below. Oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza. Because currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes, these medications are not recommended for use against influenza A infections.[15]

Table 2: Antiviral Resistance Among Influenza Viruses Worldwide, December 2010[15]

Antiviral Agent	Influenza A		Influenza B
	2009 H1N1	H3N2	B
Amantadine	Resistant	Resistant	No Activity
Oseltamivir	Susceptible	Susceptible	Susceptible
Rimantadine	Resistant	Resistant	No Activity
Zanamivir	Susceptible	Susceptible	Susceptible

Indications

Table 3. Food and Drug Administration-Approved Indications[3,4,9,10,12]

Indication	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Prophylaxis against signs and symptoms of influenza A virus infection	✔ *		✔ *	
Prophylaxis of influenza		✔ *†		✔ *‡§‖
Treatment of acute, uncomplicated illness due to influenza infection in patients two weeks of age and older who have been symptomatic for no more than two days		✔		
Treatment of drug-induced extrapyramidal reactions	✔			
Treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism and symptomatic parkinsonism	✔			
Treatment of illness caused by various strains of influenza A virus in adults			✔ *	
Treatment of uncomplicated acute illness due to influenza A and B in patients seven years of age and older who have been symptomatic for no more than two days				✔ §¶
Treatment of uncomplicated respiratory tract illness caused by influenza A virus	✔			

*Not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Immunization Practices Advisory Committee.
† In patients one year of age and older
‡ In patients five years of age and older

§ Not recommended for the treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to the risk of serious bronchospasm.
‖ Not proven effective for prophylaxis of influenza in the nursing home setting.
¶ Not proven effective for treatment of influenza in individuals with underlying airways disease.

Pharmacokinetics

Table 4. Pharmacokinetics[3,4,8,9,10,12]

Generic Name	Time to Peak Blood Levels (hours)	Protein Binding (%)	Bio-availability (%)	Active Metabolites	Renal Excretion (%)	Serum Half-Life (hours)
Amantadine	2 to 4	67	86 to 90	No	80 to 90	9 to 31
Oseltamivir	1.0 to 1.5	42 (prodrug); 3 (active metabolite)	≥75	Yes (oseltamivir carboxylate)	>99 (oseltamivir carboxylate)	1 to 3 (prodrug); 6 to 10 (active metabolite)
Rimantadine	2 to 6	40	45.6 to 117.0	No	75	25.4 to 32.0
Zanamivir	1 to 2	<10	4 to 17	No	Not reported	2.5 to 5.1

Oseltamivir is a prodrug and its pharmacological activity is provided by its active metabolite, oseltamivir carboxylate.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the influenza antivirals in Food and Drug Administration approved indications are outlined in Table 5.[16-79] Overall, the agents in this class have demonstrated efficacy for their respective indications. Although the adamantanes have demonstrated efficacy against influenza A for both prophylaxis and treatment, increasing resistance has developed over the years and treatment guidelines no longer recommend their use for current strains of influenza.[15]

Oseltamivir and zanamivir have been effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated reduced laboratory-confirmed influenza, decreased illness, fever duration, secondary complications, as well as a reduction in household contacts with influenza infection.[17-20,22,27-29,31,33,37,38,40-43,49-51,55-59,66-68] Numerous placebo-controlled trials have demonstrated the efficacy of oseltamivir and zanamivir individually; however, head-to-head trials directly comparing the agents are limited. Kawai and colleagues compared oseltamivir to zanamivir for the treatment of both influenza A and B. Results demonstrated significantly shorter fever duration in patients with influenza B who were treated with zanamivir, compared to those treated with oseltamivir.[59] Tuna et al found that for overall efficacy, oseltamivir and zanamivir had no significant difference, but temperature normalization was significantly faster in the zanamivir group (P=0.0157).[60] Limited within class comparisons prevent recommendation of one neuraminidase inhibitor over the other.

Clinical trials have demonstrated that amantadine and rimantadine are also effective in both the prophylaxis and treatment of influenza A; however, as mentioned previously, these agents are not recommended for the treatment of influenza and they should only be used in selected circumstances.[1,16,17,23-26,30,32,58,61,67,69-71]

With regard to Parkinson's disease, data from one clinical trial included in a meta-analysis demonstrated that patients receiving amantadine as monotherapy or adjuvant therapy for idiopathic Parkinson's disease achieved greater benefits in Parkinsonian symptoms severity scale scores and activity impairment scale scores compared to placebo.[72] Furthermore, for the treatment of drug-induced extrapyramidal reactions, amantadine has demonstrated efficacy in reducing dyskinesia frequency and severity, as well as motor complications in patients with Parkinson's disease.[73-79]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Influenza Prophylaxis				
Bryson et al[16] Amantadine vs placebo	DB, PRO, RCT, XO Young adults attending college	N=88 4 weeks	Primary: Gross and subtle adverse events Secondary: Not reported	Primary: Adverse events (i.e., dizziness, nervousness, and insomnia) occurred in 33% of those receiving amantadine and in 10% of those receiving placebo (P<0.005). Although adverse events were well tolerated by most subjects, six volunteers discontinued amantadine because of marked complaints. Cessation of adverse events occurred in more than half of those continuing amantadine. Sixteen students receiving amantadine had decreased performance on sustained attention tasks as compared to ones receiving placebo (P<0.05). Secondary: Not reported
Reuman et al[17] Study 1 (naturally occurring influenza): amantadine 100 mg QD vs amantadine 200 mg QD vs placebo Study 2 (experimental challenge): amantadine 50 mg QD vs	2 DB, PC, RCT Healthy hospital personnel 18 to 55 years of age	Study 1: N=476 6 weeks Study 2: N=78 13 days	Primary: Efficacy, as measured by number of influenza-like illnesses, number of laboratory-confirmed influenza cases using blood tests and viral assays from nasal washouts Secondary: Not reported	Primary: In the first study, adverse reactions were not significantly different between the group receiving 100 mg/day and the placebo group, but significantly greater in the group given 200 mg/day (P<0.009). The study authors concluded that the influenza attack rate in this study was too low to assess efficacy. In the experimental challenge study of influenza A/Beth/1/85, the prophylactic administration of 50, 100 or 200 mg/day was more effective compared to placebo in preventing influenza illness (66, 74 and 82% protection, respectively; P<0.02), and in suppressing viral replication (P=0.02). There was no significant difference between amantadine groups in influenza illness or viral shedding. Compared to the placebo group the 100 and 200 mg groups showed a significant decrease in infection rate (100 mg, 40% protection; P=0.012, 200 mg, 32% protection; P=0.045) whereas the 50 mg group did not (20% protection; P=0.187).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amantadine 100 mg QD vs amantadine 200 mg QD				Secondary: Not reported
Chik et al[18] Oseltamivir 75 mg QD for 8 weeks (for prophylaxis)	OL, OS, PRO Patients with a mean age of 14, immunocompromised through chemotherapy or bone marrow transplantation	N=32 12 weeks	Primary: Diagnosis of influenza Secondary: Not reported	Primary: Throughout the study period there were no laboratory confirmed cases of influenza infection. Secondary: Not reported
Peters et al[19] Oseltamivir 75 mg QD for 6 weeks beginning when influenza was detected locally vs placebo	DB, MC, PC, PG, RCT Frail older occupants (mean age 81, >80% vaccinated) in residential homes across the United States and Europe	N=548 1998 to 1999 influenza season	Primary: Laboratory-confirmed clinical influenza Secondary: Adverse events	Primary: Oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared to placebo (0.4 vs 4.4%; P=0.002). Of subjects vaccinated against influenza, oseltamivir was 91% effective in preventing laboratory-confirmed clinical influenza compared to placebo (0.5 vs 5.0%; P=0.003). Oseltamivir was associated with a significant reduction in the incidence of secondary complications compared to placebo (0.4 vs 2.6%; P=0.037). Secondary: A similar incidence of adverse events, including gastrointestinal events, occurred in both groups.
Welliver et al[20] Oseltamivir 75 mg QD for 7 days vs placebo	DB, PC, RCT Households with an index contact of any age, and with 2 to 8 other contacts >12 years of age; within <48 hours of symptom onset in the index	N=962 (377 households) 7 days	Primary: Proportion of contacts of an influenza-positive index contact with laboratory-confirmed clinical influenza during the dosing period;	Primary: For household contacts of infected index contacts, the incidence of laboratory-confirmed clinical influenza for those receiving oseltamivir during the seven-day prophylaxis period was 0.8 vs 12.9% for those receiving placebo. This was calculated as a protective efficacy rate of 89% (95% CI, 67 to 97; P<0.001). For households with infected index contacts, the proportion of households with at least one subsequently infected contact were 3.6% for the oseltamivir group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	contact		proportion of influenza cases in the test population as a whole Secondary: Number of households with additional influenza-related illnesses	compared to 22.8% for the placebo group. This was calculated as a protective efficacy rate of 84% (95% CI, 49 to 95; P<0.001). Data was also collected in cases where the index contact was not influenza as confirmed by laboratory tests, and in this group 0.4% of individuals taking oseltamivir came down with influenza from exposure in the community compared to 3.1% of individuals receiving placebo. Protective efficacy for these individuals exposed to influenza outside the household was calculated at 89% (95% CI, 10 to 99; P=0.009). Twenty-one of the clinical cases among the placebo recipients were infected with influenza A and 13 with influenza B. None of the clinical cases in the group of oseltamivir-treated contacts was infected with influenza A, so protective efficacy was not calculated. The protective efficacy against influenza B in contacts of all index contacts was calculated at 78.5% (P=0.02). Secondary: Frequency of individuals shedding virus and therefore more likely to transmit to others was significantly reduced in oseltamivir recipients compared to placebo recipients. The protective efficacy in contacts of an influenza positive index contact was calculated at 84% (95% CI, 57 to 95; P<0.001).
Hayden et al[21] Oseltamivir 75 mg BID for 10 days (PEP) vs oseltamivir 75 mg BID for 5 days at the time of developing illness (expectant treatment)	PG, PRO, RCT Household contacts of index cases presenting with an influenza-like illness ≥1 year of age	N=812 2000 to 2001 influenza season	Primary: Secondary spread of influenza Secondary: Not reported	Primary: PEP provided a protective efficacy of 58.5% (95% CI, 15.6 to 79.6; P=0.0114) for households against proven influenza and 68.0% (95% CI, 34.9 to 84.2; P=0.0017) for individual contacts, compared to treatment of index cases alone. No oseltamivir-resistant variants were detected in treated index cases or contacts. Secondary: Not reported
Hayden et al[22] Oseltamivir 75 mg QD for 6 weeks	DB, MC, PC, RCT Healthy, nonimmunized adults	N=1,559 1997 to 1998 influenza	Primary: Laboratory-confirmed influenza-like	Primary: The risk of influenza among subjects assigned to either QD or BID oseltamivir (1.2 and 1.3%, respectively) was lower than that among subjects assigned to placebo (4.8%; P<0.001 and P=0.001 for the comparison with QD and BID

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs oseltamivir 75 mg BID for 6 weeks vs placebo	18 to 65 years of age	season	illness Secondary: Adverse events	oseltamivir, respectively). The protective efficacy of oseltamivir in the two active-treatment groups combined was 74% (95% CI, 53 to 88) at all the sites and 82% (95% CI, 60 to 93) at sites in Virginia, where the rate of influenza infection was higher than the overall rate. For culture-proven influenza, the rate of protective efficacy in the two oseltamivir groups combined was 87% (95% CI, 65 to 96). The rate of laboratory-confirmed influenza infection was lower with oseltamivir than with placebo (5.3 vs 10.6%; P<0.001). Secondary: Oseltamivir was well tolerated but was associated with a greater frequency of nausea (12.1 and 14.6% in the QD and BID groups, respectively) and vomiting (2.5 and 2.7%, respectively) than was placebo (nausea, 7.1%; vomiting, 0.8%). The frequency of premature discontinuation of drug or placebo was similar among the three groups (3.1 to 4.0%).
Brady et al (abstract)[23] Rimantadine 100 mg QD for 6 weeks immediately after influenza A was detected in the community at each study site vs placebo	DB, PC Adult patients 18 to 55 years of age from Baltimore and Columbus communities	N=228 6 weeks	Primary: Adverse events, presence of influenza virus infection Secondary: Not reported	Primary: Only 10 (8.7%) of the 114 rimantadine-treated subjects and five (4.4%) of 114 placebo-treated recipients reported one or more adverse event. The most frequently reported adverse event in both groups was related to the gastrointestinal and central nervous systems. A total of seven rimantadine recipients and 20 placebo recipients developed influenza A infection, as documented by isolation of influenza A, a four-fold or greater rise in hemagglutination inhibition antibody titer to influenza A (H3N2) in serum, or both (seven of 112 vs 20 of 110 participants, respectively; P<0.01). Influenza A/Leningrad/87-like (H3N2) virus was recovered from five placebo recipients but was not recovered from any of the rimantadine recipients. Altogether, 19 rimantadine recipients and 21 placebo recipients developed a respiratory illness during the study, but influenza A infection was documented in only 15 ill volunteers.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Rimantadine recipients developed influenza A illness significantly less often than did placebo recipients (one of 112 vs seven of 110 recipients respectively; P<0.04). Secondary: Not reported
Crawford et al[24] Rimantadine vs placebo	DB, PC, RCT Children (1 to 18 years of age) and adult members from 29 families	N=110 A naturally occurring outbreak of influenza A (H3N2)	Primary: Efficacy against influenza A infection and associated illness and the prevention of transmission of infection to adult members of the child's family Secondary: Adverse events	Primary: Influenza infections, defined as a positive viral throat culture or a four-fold increase in antibody titer, occurred in 31% of children in the placebo group and 7.4% of children in the rimantadine group (P=0.026). Clinical illness with laboratory evidence of influenza infection occurred in 24.1% of children in the placebo group and none of the children in the rimantadine group (P=0.007). Secondary: Rimantadine was well-tolerated by the children, with no significant difference in reported adverse events between the placebo and rimantadine groups.
Hayden et al[25] Rimantadine 200 mg QD for 10 days vs placebo	DB, PC, RCT Household members of patients with influenza A	N=237 (families) Two influenza seasons	Primary: Development of illness and resistance Secondary: Not reported	Primary: Among households with documented influenza A infections, symptomatic illness occurred in one or more contacts in 10 of 28 families treated with rimantadine and in 10 of 209 families treated with placebo. Asymptomatic secondary influenza A infections were found in five families assigned to receive rimantadine and in four families assigned to receive placebo. Rimantadine-resistant strains of influenza A (H3N2 subtype) with mutations consisting of single amino acid changes in the M2 protein (residue 27, 30, or 31) were recovered from eight index patients and five contacts treated with rimantadine. There was apparent transmission of drug-resistant strains of virus in six contacts with secondary illnesses in five families. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Monto et al[26] Rimantadine 100 mg QD vs rimantadine 200 mg QD vs placebo Regimens were at a ratio of 2:2:1.	DB, XO Elderly residents of 10 nursing homes in southern lower Michigan	N=328 8 weeks	Primary: Adverse events, influenza-like illness, laboratory-confirmed clinical influenza, influenza virus infection Secondary: Not reported	Primary: Overall, 33% of study participants experienced at least one potential adverse events. Participants in all three groups were equally likely to experience each of the specified symptoms. Efficacy analyses were carried out on 68 vaccinated residents of two nursing homes with demonstrated influenza activity. The administration of rimantadine at both dosages was associated with a decrease in the likelihood of clinical influenza-like illness and laboratory-confirmed influenza infection when compared to the administration of placebo, though no difference was statistically significant. No additional benefit of a 200 mg dose was observed compared to the 100 mg dose. When data for the 100 and 200 mg/day groups were combined and compared to data for the group receiving placebo, the efficacy of rimantadine in reducing the risk of clinical influenza-like illness was estimated to be 58% (P=0.079). Secondary: Not reported
Hayden et al[27] Zanamivir 10 mg inhaled QD for 10 days in household contacts as prophylaxis vs placebo If an influenza-like illness developed in one	DB, PC Families with two to five members and at least one child who was 5 years of age or older	N=1,158 1998 to1999 influenza season	Primary: The proportion of families with at least one household contact with symptomatic, laboratory-confirmed influenza Secondary: Zanamivir-resistant variants	Primary: The proportion of families with at least one initially healthy household contact in whom influenza developed was smaller in the zanamivir group than in the placebo group (four vs 19%; P<0.001); the difference represented a 79% reduction in the proportion of families with at least one affected contact. Secondary: Zanamivir provided protection against both influenza A and influenza B. A neuraminidase-inhibition assay and sequencing of the neuraminidase and hemagglutinin genes revealed no zanamivir-resistant variants. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5.0 vs 7.5 days; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
member, the family was randomly assigned to receive either inhaled zanamivir or placebo. Infected family members (index) were treated with either 10 mg of inhaled zanamivir or placebo.			and the median duration of symptoms in the index cases	
Monto et al[28] Zanamivir 10 mg inhaled QD for 10 days in household contacts as prophylaxis vs placebo Index patients received relief medication only.	DB, MC, PC, RCT Once a person with a suspected case of influenza was identified (index patient), treatment of all other household members (contacts) ≥5 years old was initiated; eligible households were composed of 2 to 5 members, with at least 1 adult >18 years old and 1 child 5 to17 years old	N=1,778 11 months	Primary: Household contacts that developed symptomatic, laboratory-confirmed influenza Secondary: Not reported	Primary: Four percent of zanamivir-treated households and 19% of placebo-treated households had at least one contact who developed symptomatic, laboratory-confirmed influenza (P<0.001), representing 81% protective efficacy (95% CI, 64 to 90). Protective efficacy was similarly high for individuals (82%) and against both influenza types A and B (78 and 85%, respectively, for households). Zanamivir was well tolerated and was effective in preventing influenza types A and B within households where the index patient was not treated. Secondary: Not reported
Monto et al[29] Zanamivir 10 mg inhaled QD for 4 weeks vs placebo	DB, PC, RCT Healthy adults 18 to 69 years of age	N=1,107 1997 to1998 influenza season	Primary: Laboratory-confirmed clinical influenza occurrence Secondary: Adverse events	Primary: Zanamivir was 67% efficacious (95% CI, 39 to 83; P<0.001) in preventing laboratory-confirmed clinical influenza meeting the case definition and 84% efficacious (95% CI, 55 to 94; P=0.001) in preventing laboratory-confirmed illnesses with fever. All influenza infections occurring during the season, with or without symptoms, were prevented with an efficacy of 31% (95% CI, 4 to 50; P=0.03). Secondary: The nature and incidence of adverse events in the zanamivir group did not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				differ from the placebo group. Adverse events thought by the investigators to be potentially drug-related were observed in 27 (5%) patients in the placebo group and 30 (5%) patients in the zanamivir group. Potential adverse events that were considered severe were seen in one (<1%) patient in the placebo group and one (<1%) patient in the zanamivir group.
Dolin et al[30] Amantadine 100 mg BID for 6 weeks vs rimantadine 100 mg BID for 6 weeks vs placebo	DB, PC, RC Healthy non-vaccinated adults aged 18 to 45 who volunteered for the study	N=450 6 weeks	Primary: Efficacy, defined as number of influenza-like illnesses, and number of laboratory-confirmed influenza cases Secondary: Adverse events	Primary: Influenza-like illness occurred in 41% of the subjects receiving placebo, 14% of those receiving rimantadine and 9% of those receiving amantadine (P<0.001 for either drug vs placebo). Laboratory-documented influenza occurred in 21% of placebo recipients, 3% of rimantadine recipients and 2% of amantadine recipients (P<0.001 for either drug vs placebo). These findings represent efficacy rates of 85% for rimantadine and 91% for amantadine, as compared to placebo. Secondary: More recipients of amantadine (13%) than recipients of rimantadine (6%; P<0.05) or placebo (4%; P<0.01) withdrew from the study because of central nervous system adverse events.
Gravenstein et al[31] (abstract) Zanamivir 10 mg inhaled QD for 14 days vs standard of care (rimantadine 100 mg for influenza A or placebo for influenza B) QD for 14 days	DB, PRO, RCT Nursing home residents	N=482 14 days for 3 influenza seasons (1997 to 2000)	Primary: The proportion of randomized subjects developing symptomatic, laboratory-confirmed influenza during prophylaxis Secondary: Not reported	Primary: Symptomatic, laboratory-confirmed influenza occurred in 3% of zanamivir subjects and 8% of rimantadine subjects during chemoprophylaxis (P=0.038; additional protective efficacy for zanamivir over rimantadine was 61). Since only 25 subjects were randomized during two influenza B outbreaks and none developed influenza, the influenza B data was excluded from further analysis. Zanamivir was well tolerated and unassociated with emergence of resistant virus; rimantadine-resistant variants were common. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jackson et al[32] Amantadine vs oseltamivir vs zanamivir vs placebo or no treatment	SR Patients receiving seasonal prophylaxis or post-exposure prophylaxis	N=Not reported (≈20,000) Duration varied (5 days to 9 weeks)	Primary: Efficacy Secondary: Complications prevented, hospitalization prevented, length of influenza illness, time to return to normal activities, adverse events, vaccination status, antiviral resistance	Primary: Use of amantadine in seasonal prophylaxis Owing to low attack rates during trial periods, evidence for amantadine against symptomatic, laboratory-confirmed influenza in seasonal prophylaxis was limited. One trial demonstrated a nonsignificant preventative effect among healthy adults (RR, 0.40; 95% CI, 0.08 to 2.03). Use of amantadine in healthy adults appeared to result in no difference in the incidence of acute respiratory illness between treatment groups. Use of oseltamivir in seasonal prophylaxis Oseltamivir was efficacious against symptomatic, laboratory-confirmed influenza in healthy adults (RR, 0.24; 95% CI, 0.09 to 0.51; pooled estimate from two trials reported as a single publication). A protective effect of oseltamivir against symptomatic, laboratory-confirmed influenza was notable in one trial among frail elderly patients living in residential care (98% with concomitant disease) (RR, 0.08; 95% CI, 0.01 to 0.63). Use of zanamivir in seasonal prophylaxis A protective efficacy of 68% with zanamivir in healthy adults was demonstrated in one trial (RR, 0.32; 95% CI, 0.17 to 0.63; calculated by assessment group). Another trial demonstrated zanamivir to be efficacious in at-risk adolescents and adults (RR, 0.17; 95% CI, 0.07 to 0.44), with a nonsignificant preventative effect in older adults (1/946 with zanamivir vs 5/950 with placebo; RR, 0.20; 95% CI, 0.02 to 1.72). Use of amantadine in post-exposure prophylaxis One trial evaluating outbreak control in a boarding school setting demonstrated that amantadine was effective in preventing symptomatic, laboratory-confirmed influenza in healthy adolescents (RR, 0.10; 95% CI, 0.03 to 0.34). In another trial, amantadine demonstrated protective efficacy (RR, 0.59; 95% CI, 0.49 to 0.70) and ability to shorten the duration (P<0.05) and severity (P<0.01) of clinical influenza. Of note, the reporting of this trial was unclear. Use of oseltamivir in post-exposure prophylaxis A protective efficacy of 81% with oseltamivir against symptomatic, laboratory-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				confirmed influenza in household contacts of mixed composition (adults plus children at least one year of age and adults plus children at least 12 years of age) was demonstrated (RR, 0.19; 95% CI, 0.08 to 0.45; pooled estimate of two trials). Post-exposure prophylaxis in pediatric patients at least one year of age was demonstrated to have a preventative effect against symptomatic, laboratory-confirmed influenza in one trial (RR, 0.36; 95%, 0.15 to 0.84). Use of zanamivir in post-exposure prophylaxis Zanamivir was efficacious in preventing transmission of symptomatic, laboratory-confirmed influenza in households of mixed composition (adults and children at least five years of age, unvaccinated adolescents and adults 13 to 65 years of age) based on three trials (RR, 0.21; 95% CI, 0.13 to 0.33). Evidence for outbreak control in elderly adults in long term care was more limited, with a nonsignificant protective effect against symptomatic, laboratory-confirmed influenza demonstrated (RR, 0.68; 95% CI, 0.33 to 1.27), whereby all cases occurred in unvaccinated patients (calculated by assessment group). Secondary: No evidence relating to health-related quality of life or mortality was identified for amantadine, oseltamivir and zanamivir. Use of amantadine in seasonal prophylaxis No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis. Use of oseltamivir in seasonal prophylaxis One trial demonstrated that oseltamivir was associated with a nonsignificant 78% relative reductions in secondary complications (no further details presented) among at-risk elderly adults with laboratory confirmed influenza (P=1.14). Use of zanamivir in seasonal prophylaxis Significantly less work absence was reported among patients receiving zanamivir vs control (mean hours lost, 0.6 vs 1.4; P=0.001). Total productive time lost was also less with zanamivir (1.8 vs 3.0 hours; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Use of amantadine in post-exposure prophylaxis Two trials provided limited evidence that identified milder influenza illness of shorter duration with the use of amantadine. The severity of symptoms was reported as 56% mild and 9% severe with amantadine, and 38% mild and 19% severe with placebo (P<0.01 for severe symptoms, P<0.001 for mild symptoms). Mean duration of illness was shorter with amantadine compared to placebo (P<0.05). Use of oseltamivir in post-exposure prophylaxis In one trial with a population of mixed composition (adults plus children at least one year of age), the proportion of contacts with laboratory confirmed influenza with at least one secondary complication (e.g., bronchitis, pneumonia, lower respiratory tract infection, otitis media, sinusitis) was equivalent among post-exposure patients and those receiving control who received expectant treatment upon the onset of influenza-like illness (7 vs 5%); however, the more severe respiratory complications (e.g., bronchitis, pneumonia) occurred among the expectant treatment group. In this trial, the mean duration of illness in contacts was shorter with oseltamivir post-exposure prophylaxis vs those receiving treatment on influenza onset (5.5 vs 39.8 hours; P=0.103). Fewer contacts with laboratory confirmed influenza receiving oseltamivir post-exposure prophylaxis were bedbound compared to patients receiving treatment at influenza onset (7 vs 28%; P value not reported), demonstrating a milder form of disease. Use of zanamivir in post-exposure prophylaxis In one trial, significantly fewer households receiving zanamivir reported a contact developing a complication of laboratory confirmed influenza (2 vs 6%; P=0.01). In another trial, complications of symptomatic, laboratory-confirmed influenza (adverse events consistent with complications of influenza among patients with symptomatic, laboratory-confirmed influenza) during the first 28 days following post-exposure prophylaxis initiation were lower with zanamivir vs placebo (5 vs 6%; P=0.653). In a third trial, the proportion of cases with complications requiring antibiotics was lower with zanamivir compared to placebo (5 vs 8%; P value not reported). Furthermore, among household contacts with laboratory confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 and 8.0 days with zanamivir and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo (P value not reported). In another trial, mean duration of significant influenza-like symptoms was also observed to be shorter with zanamivir vs placebo (0.2 vs 0.6 days; P=0.016). No strong evidence for a higher incidence of adverse events in treatment groups compared to control was identified for amantadine, oseltamivir or zanamivir. Few serious drug-related adverse events and drug-related withdrawals were reported. Limited evidence was identified relating to the impact of vaccination status on the efficacy of amantadine prophylaxis. The protective efficacy of oseltamivir in elderly adults in seasonal prophylaxis when analyzed among vaccinated patients only was found to be comparable with the protective efficacy among the trial population as a whole (protective efficacies of 91 and 92%, respectively). In one trial, overall the use of zanamivir in seasonal prophylaxis in healthy adults (18 to 64 years of age) yielded a 68% (95% CI, 37 to 83) protective efficacy against symptomatic, laboratory-confirmed influenza. Among unvaccinated patients, the protective efficacy appeared to be lower (60%; 95% CI, 24 to 80). In another trial, for the use of zanamivir in seasonal prophylaxis in at-risk adults and adolescents, comparable effects were observed, with RRs of 0.17 (95% CI, 0.02 to 1.41) and 0.17 (95% CI, 0.0 to 0.58) of developing symptomatic, laboratory-confirmed influenza in vaccinated and unvaccinated patients, respectively. Of the cases of symptomatic, laboratory-confirmed influenza that were observed in another trial of zanamivir in outbreak control, all occurred in unvaccinated patients. No evidence of reduced sensitivity to tested viral isolates to oseltamivir or zanamivir was obtained in included trials. None of the amantadine prophylaxis trials included reported the assessment of sensitivity of influenza isolates to amantadine.
Influenza Treatment				
Aoki et al[33] Oseltamivir 75 mg BID for 5 days	MC, OL Patients (12 to 70 years of age) presenting within 48	N=1,426 1999 to 2000 influenza season	Primary: Illness duration Secondary: Duration of fever,	Primary: Earlier intervention was associated with shorter illness duration (P<0.0001). Initiation of therapy within the first 12 hours after fever onset reduced the total median illness duration by 74.6 hours (3.1 days; 41.0%) more than intervention at 48 hours.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hours of the onset of influenza symptoms		severity of symptoms, time to return to baseline activity	Secondary: The early administration of oseltamivir further reduced the duration of fever (P=0.0115), severity of symptoms (P=0.0023) and the times to return to baseline activity (P=0.001).
Machado et al[34] Oseltamivir 75 mg BID for 5 days	OL, PRO Patients with a proven upper or lower respiratory tract influenza infection detected by direct immunofluorescence assay	N=66 1 year	Primary: Complications of influenza Secondary: Not reported	Primary: The percent of patients who developed influenza-related pneumonia after the initiation of oseltamivir within 48 hours of symptoms appearing was 5.1% and no patients died of influenza. Secondary: Not reported
Ebell et al[35] Oseltamivir vs placebo	MA Adults with suspected or confirmed influenza	N=4,769 Duration not reported	Primary: Mean duration of symptoms, likelihood of complications and likelihood of hospitalization Secondary: Not reported	Primary: Treatment with oseltamivir was associated with a mean reduction in the duration of symptoms by 20.7 hours in the ITT population (95% CI, 13.3 to 28.0). The mean reduction in the duration of symptoms was 25.4 hours for the ITTI population (95% CI, 17.2 to 33.5). There was no significant difference between the oseltamivir and placebo treatment groups regarding the likelihood of any hospitalization in the ITT population (RD, 0.1%; 95% CI, -0.5 to 0.6). Moreover, no difference between groups were reported in the ITT population with regard to hospitalizations due to respiratory complications, sepsis or dehydration (RD, 0.0%; 95% CI, -0.5 to 0.4). Pneumonia was less common among patients receiving oseltamivir compared to placebo in the ITTI population (RD, -0.9%; 95% CI, -1.7 to -0.1); however, a significant reduction in the likelihood of pneumonia was not observed among patients in the ITT population (RD, -0.6%; 95% CI, -1.7 to 0.4). The composite outcome of otitis media, sinusitis, pneumonia and bronchitis was significantly less frequent among patients receiving oseltamivir compared to placebo in the ITTI population (RD, -2.8%; 95% CI, -4.9 to -0.6). If acute bronchitis is excluded, there was no difference between groups in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				likelihood of the combined outcome (RD, -0.1%; 95% CI, -1.7 to 1.5). Data were not reported for these outcomes in the ITT population. Secondary: Not reported
Sugaya et al[36] Oseltamivir BID for 5 days (weight-based dosing) vs control (did not receive oseltamivir)	OL Children aged 1 to 15 years of age presenting to outpatient clinics within 48 hours of onset of symptoms	N=127 (influenza A) N=362 (influenza B) 5 days	Primary: Total febrile period, duration of fever, effectiveness according to age, effectiveness and history of vaccination, virus shedding Secondary: Not reported	Primary: When comparing the study participants with influenza A to those with influenza B, there was a significant difference in the mean duration of febrile period (2.19 vs 4.44 days; P<0.001). In patients with influenza B, the mean duration of febrile period significantly differed between the patients treated with oseltamivir and the control patients (2.98 vs 5.55 days; P<0.001). The mean duration of fever after the initiation of therapy was 1.31 days with influenza A patients compared to 2.18 days with influenza B patients (P<0.001). For patients with influenza B, the duration of fever was significantly longer in children one to five years of age (2.37 days) than in children six to 10 years of age (1.97 days; P=0.013) and 11 to 15 years of age (1.54 days; P=0.006). The difference between children six to 10 and 11 to 15 years of age was not significant (P=0.14). There was a significant difference in the duration of fever in the two younger groups of children between the patients with influenza A and B (children one to five, 1.42 vs 2.37 days; P<0.001 and children six to 10, 1.23 vs 1.97 days; P<0.001). There was no significant difference in duration of fever with influenza A vs influenza B in the group of children aged 11 to 15 (P=0.54). There was no significant difference either for the total population or for the subgroups by age in the duration of fever between patients with influenza A who had been vaccinated and those who had not (1.36 vs 1.36 days). There was a significant difference in mean virus titers two days after the start of oseltamivir between the influenza A and influenza B groups (0.61 vs 2.84;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.001). Secondary: Not reported
Singh et al[37] Oseltamivir 75 mg BID vs placebo	MA Individuals aged 13 to 97 presenting within 36 hours of onset of influenza symptoms	N=2,413 Specific duration varied	Primary: Alleviation of illness, return to normal health status, ability to perform usual activities, normal sleep patterns, symptom improvement, duration of illness Secondary: Not reported	Primary: When compared to placebo, the time to alleviation of illness was reduced by 19% (median duration, 100.6 [95% CI, 94.8 to 104.7] vs 124.5 hours [95% CI, 117.7 to 132.3]; P<0.00010). When compared to placebo individuals who received oseltamivir returned to normal health status, regained ability to perform usual activities and regained normal sleep patterns significantly faster (P values not reported). When compared to placebo, treatment with oseltamivir significantly reduced fatigue by 29% and myalgia by 26% (P<0.0001). More placebo- than oseltamivir-treated patients (57%) remained febrile after 48 hours of treatment (no P value reported). The median duration of acute febrile illness was significantly shortened by use of oseltamivir when compared to placebo use in patients with cardiac disease (44.0 vs 64.7 hours; P=0.026) and chronic obstructive pulmonary disease (37.9 vs 53.8 hours; P=0.004). Secondary: Not reported
Kawai et al[38] Oseltamivir 75 mg BID for 5 days vs placebo	MC, PRO Patients who reported influenza-like illness	N=1,818 (influenza A) N=1,485 (influenza B) 5 days	Primary: Duration of fever Secondary: Not reported	Primary: Patients with influenza A and influenza B who were treated with oseltamivir had a significantly shorter duration of fever compared to patients who were not treated with oseltamivir (P<0.001). The duration of fever was significantly longer among oseltamivir-treated patients who had influenza B compared to influenza A, respectively (65.4 vs 47.9 hours; P<0.001). For patients with influenza B compared to patients with influenza A, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				duration of fever, measured from the time at which the first dose of oseltamivir was administered, was significantly longer at all-time points (P<0.001). For patients with influenza B compared to patients with influenza A, the duration of fever from the time at which the first dose of oseltamivir was administered was significantly longer in all age groups (P<0.001). Secondary: Not reported
Kaiser et al[39] Oseltamivir 75 mg BID for 5 days vs placebo	MA Patients 13 to 97 years of age with influenza like illnesses	N=3,564 28 days	Primary: The occurrence of lower respiratory tract complications, requiring intervention Secondary: Hospitalizations, upper respiratory tract complications, overall antibiotic use	Primary: Among influenza-infected patients, oseltamivir reduced the incidence of lower respiratory tract complications leading to antibiotic intervention by 55% compared to placebo (4.6 vs 10.3%; P<0.001). Secondary: The overall percentage of patients hospitalized for any cause was 1.7% in the placebo group compared to 0.7% in the oseltamivir group (59% reduction; P=0.02). A reduction of 50% in overall hospitalizations was seen in the oseltamivir-treated, influenza-infected at-risk patients compared to placebo treated, influenza-infected at-risk patients (1.6 vs 3.2%; P=0.17). The overall incidence of respiratory events following influenza infection was reduced by 28% in the oseltamivir group when compared to the placebo group (11.9 vs 16.9%; P=0.001). No difference was observed in physician diagnosed upper respiratory tract complications leading to antibiotic use between the two treatment groups (P value not reported).
Fry et al[40] Oseltamivir BID for 5 days	DB, RCT Patients median age of 5 with a positive rapid influenza test	N=1,190 Duration varied	Primary: Duration of clinical illness and viral shedding in patients treated	Primary: The median duration of symptoms was shorter in the oseltamivir group (three days) than in the placebo group (four days; P=0.01). When stratified by timing of treatment initiation, in participants enrolled 48

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	identified by surveillance of households		less than and more than 48 hours since illness onset and the frequency of oseltamivir resistance during treatment Secondary: Not reported	hours or longer since illness onset, the median duration of symptoms was similar in both groups (oseltamivir, three days; placebo, three days; P=0.04). The median duration of symptoms was reduced by one day in the group given oseltamivir who were enrolled less than 48 hours since symptom onset compared with those given placebo, but this difference was NS. In those with all swab specimens (n=1,134), oseltamivir significantly reduced virus isolation on days two (placebo, 374 [66%] vs oseltamivir, 321 [56%]; difference, 15.2%; 95% CI, 9.5 to 20.8; P=0.0004), four (241 [43%] vs 174 [30%]; difference, 30.2%; 95% CI, 24.6 yo 35.8; P<0.0001), and seven (68 [12%] vs 36 [6%]; difference, 47.5%; 95% CI, 44.2 to 50.8; P=0.0009). In participants enrolled 48 hours or longer since illness onset, oseltamivir treatment significantly reduced virus isolation on days two and four, but not day seven. In participants enrolled less than 48 hours since illness onset, oseltamivir treatment significantly reduced virus isolation on days two, four, and seven. The emergency of resistance to oseltamivir during treatment was rare overall (<1%) and in influenza A H1N1 viruses (3.9%). Secondary: Not reported
Jefferson et al[41] Oseltamivir	MA PC, RCTs, on adults and children who had confirmed or suspected exposure to natural influenza	N=43 trials Duration varied	Primary: Time to first alleviation of symptoms, influenza outcomes, complications,	Primary: In treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI, 8.4 to 25.1; P<0.001). There was no effect in children with asthma, but there was an effect in otherwise healthy children (mean difference, 29 hours, 95% CI, 12 to 47; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			admissions to hospital, and adverse events Secondary: Not reported	In treatment trials there was no difference in admissions to hospital in adults (risk difference, 0.15%; 95% CI, -0.91 to 0.78; P=0.84) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference, 1.00%; 0.22 to 1.49; number needed to treat to benefit, 100; 95% CI, 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for "pneumonia," and no clinical study reports reported laboratory or diagnostic confirmation of "pneumonia." The effect on unverified pneumonia in children and for prophylaxis was NS. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. Oseltamivir in the treatment of adults increased the risk of nausea (risk difference, 3.66%; 0.90 to 7.39; number needed to treat to harm, 28; 95% CI, 14 to 112) and vomiting (4.56%, 2.39 to 7.58; 22, 14 to 42). In treatment of children, oseltamivir induced vomiting (5.34%, 1.75 to 10.29; 19, 10 to 57). In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% (3.05%, 1.83 to 3.88; number needed to treat to benefit, 33; 26 to 55) and households (13.6%, 9.52 to 15.47; number needed to treat to benefit, 7; 6 to 11) based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission. In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods (risk difference, 1.06%; 0.07 to 2.76; number needed to treat to harm, 94; 36 to 1,538) and there was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) BID (P=0.038). In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (risk difference, 3.15%; 0.88 to 5.78; number needed to treat to harm, 32; 18 to 115), renal events with treatment (0.67%, -0.01 to 2.93), and nausea while receiving treatment (4.15%, 0.86 to 9.51; number needed to treat to harm, 25; 11 to 116). Secondary: Not reported
Bueno et al[42] Oseltamivir vs no treatment	MC, RETRO Children admitted to the hospitals with confirmed influenza infections	N=287 Duration varied	Primary: Fever duration, oxygen support, antibiotics administration, length of hospital stay, intensive care admission and bacterial complications Secondary: Not reported	Primary: There were no significant differences between treated and untreated patients in days of fever after admission (1.7+2.0, 2.1+2.9; P>0.05), length of stay (5.2+3.6, 5.5+3.4; P>0.05), days of hypoxia (1.6+2.3, 2.1+2.9; P>0.05), diagnosis of bacterial pneumonia (10%, 17%; P>0.05), intensive care admission (6.5%, 1.5%; P>0.05) or antibiotic prescription (44%, 51%; P>0.05). There were no differences when the population was stratified by age (below or over one year) or by the presence or absence of asthma. Secondary: Not reported
Whitley et al[43] Oseltamivir liquid 2 mg/kg/dose BID for 5 days vs	DB, PC, RCT Children 1 through 12 years of age with fever and a history of cough or coryza <48 hours duration	N=695 1998 to 1999 influenza season	Primary: Time to resolution of illness including mild/absent cough and coryza, return to normal activity and euthermia	Primary: Among infected children, the median duration of illness was reduced by 36 hours (26%) in oseltamivir recipients compared to placebo recipients (101 [95% CI, 89 to 118] vs 137 hours [95% CI, 125 to 150]; P<0.0001). Oseltamivir treatment also reduced cough, coryza and duration of fever. New diagnoses of otitis media were reduced by 44% (12 vs 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Adverse events	oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; P=0.03) recipients. Secondary: Oseltamivir therapy was generally well-tolerated, although associated with an excess frequency of emesis (5.8%). Discontinuation because of adverse events was low in both groups (1.8% with oseltamivir vs 1.1% with placebo).
Hayden et al[44] Rimantadine 200 mg QD for 5 days vs placebo	DB, PC, RCT Culture-proven influenza A infection caused by an A/Bangkok/1/79 (H3N2)-like virus; treatment was started within 48 hours of onset of symptoms	N=14 5 days	Primary: Viruses in nasal secretions Secondary: Maximal daily temperatures in influenza A (H3N2) infected students, duration of temperature, systemic and respiratory illness symptom scores	Primary: Rimantadine recipients had a prompt reduction in virus titers by treatment day two and had significantly lower titers than did placebo recipients on days two through four. During treatment days two through five, 23 of the 24 (96%) specimens from placebo recipients yielded the virus, compared to 16 of the 26 (62%) rimantadine recipients (P<0.01). Secondary: Rimantadine-treated patients defervesced rapidly and had significantly lower mean maximum temperatures on treatment days two and three. On treatment day three, all seven rimantadine recipients were afebrile (with a maximum oral temperature ≤99°F), compared to none of the seven placebo recipients (P<0.01). The mean ± standard deviation duration of fever (temperature, >99°F) from the onset of therapy was 31±22 hours in the rimantadine group, compared to 68±8 hours in the placebo group (P<0.01). The resolution of both respiratory and systemic symptoms tended to be more rapid in rimantadine than in placebo recipients, respectively. Rimantadine recipients had significantly lower systemic symptom scores on treatment days three and four (4±3, 4±2 vs placebo 10±4, 9±4, P<0.01 for both).
Johny et al[45] Zanamivir 10 mg BID until excretion of virus ceased	OL Patients post allograft with diagnosed influenza	N=7 5 to 44 days	Primary: Toxicity, morbidity Secondary: Not reported	Primary: With the administration of zanamivir there were no toxicity attributes noted and there was no mortality seen in the seven patients (P value not reported). Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
No authors listed[46] MIST Zanamivir 10 mg inhaled BID for 5 days vs placebo	DB, MC, RCT Healthy individuals 12 years of age or older presenting with influenza-like illness of 36 hours duration or less	N=455 28 days	Primary: Length of time to alleviation of clinically important symptoms including absence of fever, mild headache, cough, myalgia and sore throat for 24 hours Secondary: Length of time to return to normal activities, mean symptom scores, sleep disturbance, use of relief medications, rate of complications and associated use of antibiotics	Primary: Zanamivir significantly shortened the time to alleviation of symptoms in the intention-to-treat population compared to placebo (5.0 vs 6.5 days; P=0.011). This 1.5 day benefit was also seen for influenza-positive patients (4.5 vs 6.0 days; P=0.004). In patients who were febrile and received zanamivir, symptoms were decreased two days earlier than in those who received placebo (P<0.001) in the intention-to-treat and influenza-positive patient groups. Influenza-positive patients treated with zanamivir had significantly less severe symptoms overall on days one to14 than those on placebo (P<0.05). High-risk patients had significantly fewer complications than those on placebo (P=0.004) and fewer high risk patients needed antibiotic medication to treat those complications (P=0.025). Secondary: When zanamivir recipients were compared to patients on placebo, return to normal activities, sleep disturbances, complication rates, and associated use of antibiotics were all less in the intention-to-treat and influenza-positive populations, but the differences were not significant.
Hedrick et al[47] Zanamivir 10 mg inhaled BID for 5 days vs placebo	DB, MC, PC, PG, RCT Children 5 to 12 years of age with influenza-like symptoms for ≤36 hours	N=471 1998 to 1999 influenza season	Primary: Alleviation of symptoms Secondary: Return to normal activities, use of relief medications, adverse events	Primary: A total of 346 (73%) patients were influenza-positive by culture, serology or polymerase chain reaction (65% influenza A, 35% influenza B). Zanamivir reduced the median time to symptom alleviation by 1.25 days compared to placebo among patients with confirmed influenza infection (P<0.001). Secondary: Zanamivir-treated patients returned to normal activities significantly faster than placebo treated patients (influenza-positive population; P=0.022, intent-to-treat population; P=0.019). The zanamivir-treated patients also took significantly fewer relief medications than those treated with placebo in the influenza-positive (P=0.005) and intent-to-treat (P=0.016) populations. Zanamivir was well-tolerated, demonstrating adverse event profiles similar to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				those of placebo and no clinically significant changes in laboratory findings. Adverse events were reported during treatment for 21% for patients in the zanamivir group and 26% of patients in the placebo group.
Lalezari et al[48] Zanamivir 10 mg BID for 5 days vs placebo	MA High risk patients with confirmed influenza	N=321 21 to 28 days	Primary: Time to return to normal activities, median time to alleviation of symptoms Secondary: Not reported	Primary: A treatment benefit of 2.5 days was seen with the zanamivir-treated high risk patients compared to the placebo-treated high risk patients (P=0.015). Patients returned to normal activities three days earlier (P=0.022) and had an 11% reduction (P=0.0.9) in the median total symptom score over one to five days of treatment with zanamivir compared to treatment with placebo. The incidence of complications requiring antibiotic use was reduced by 43% with treatment with zanamivir compared to treatment with placebo (P=0.045). Adverse events were similar between the treatment groups (P value not reported). Secondary: Not reported
Hiba et al[49] Oseltamivir 75 mg BID for 5 days (early treatment) vs oseltamivir 75 mg BID for 5 days (late treatment, initiation later than 48 hours after symptom onset)	OS, RETRO All adults with laboratory-confirmed pandemic 2009 influenza A (H1N1) in three hospitals in central Israel between 22 July 2009 and the end of the influenza pandemic in January 2010	N=449 5 days	Primary: Influenza complications with early vs late oseltamivir treatment (pulmonary infiltrates visualized on chest X-ray or CT scan, documentation of hypoxia [arterial saturation, 90%], mechanical ventilation, intensive care unit	Primary: Early treatment with oseltamivir was associated with fewer complications as defined by the primary outcome (35.4 vs 157.7% late; P<0.001). On multivariable analysis, late initiation of oseltamivir remained significantly associated with complications (OR, 2.37; 95% CI, 1.52 to 3.70). Secondary: Early oseltamivir was associated with a lower rate of all secondary outcomes. Any complication developing after admission occurred in 15 (7.9%) of the early oseltamivir treated patients compared to 42 (16.2%) of the late treated patients (P=0.010). Any complication developing after the start of oseltamivir occurred in 13 (6.9%) of the early oseltamivir treated patients compared to 33 (12.7%) of the late treated patients (P=0.045). In the adjusted analysis, initiation of oseltamivir >48 hours after admission was significantly associated with complications developing after admission (OR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			admission, need for hemodynamic support, or in-hospital death) Secondary: Events occurring only after initiation of oseltamivir and those presenting after admission	4.09; 95% CI, 1.55 to 10.80). Early oseltamivir was also associated with a lower rate of most individual components of the composite primary outcome, including in-hospital mortality (1/180 [0.5%] patients in the early oseltamivir treated patients compared to 13/260 [5.0%] in the late treated patients [P=0.006]). Other individual components of the composite primary endpoint include: pneumonia, 22.2% early oseltamivir vs 46.9% late oseltamivir (P<0.001); hypoxemia, 20.1% early oseltamivir vs 28.1% late oseltamivir (P=0.053); intensive care unit admission, 3.2% early oseltamivir vs 9.2% late oseltamivir (P=0.011); mechanical ventilation, 3.2% early oseltamivir vs 8.1% late oseltamivir (P=0.031); and number of hospitalization days for patients discharged alive, five early oseltamivir vs seven late oseltamivir (P=0.001).
Nicholson et al[50] Oseltamivir 75 mg BID for 5 days vs oseltamivir 150 mg BID for 5 days vs placebo	RCT Adults with naturally acquired laboratory-confirmed influenza with febrile influenza-like illness of up to 36 hours duration	N=726 3 months	Primary: Time to resolution of illness Secondary: Symptom scores, viral shedding, health, activity, sleep quality, and tolerability	Primary: Duration of illness was significantly shorter by 29 hours (25% reduction, median duration 87.4 hours; 95% CI, 73.3 to 104.7; P=0.02) with oseltamivir 75 mg and by 35 hours (30% reduction, 81.8 hours; 95% CI, 68.2 to 100.0; P=0.01) with oseltamivir 150 mg, both in comparison to placebo (116.5 hours; 95% CI, 101.5 to 137.8). The effect of oseltamivir was apparent within 24 hours of the start of treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated 43 hours (37% reduction) and 47 hours (40% reduction) earlier with oseltamivir 75 and 150 mg, respectively, compared to placebo (for 75 mg, time to symptom alleviation was 74.5 hours; 95% CI, 68.2 to 98.0; P=0.02, for 150 mg, time to symptom alleviation was 70.7 hours; 95% CI, 54.0 to 89.4; P=0.01, for placebo, time to symptom alleviation was 117.5 hours; 95% CI, 103.0 to 143.8). Secondary: Oseltamivir was associated with lower symptom scores, less viral shedding, and improved health, activity, and sleep quality, and was well tolerated.
Treanor al[51]	DB, MC, RCT	N=629	Primary: Duration of illness,	Primary: The median durations of illness were 103.3 hours (4.3 days) in the placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oseltamivir 75 mg BID for 5 days vs oseltamivir 150 mg BID for 5 days vs placebo for 5 days	Adults aged 18 to 65 years presenting within 36 hours of onset of influenza symptoms; patients presented with oral temperature 38ºC or higher plus 1 or more respiratory symptom including cough, sore throat or nasal symptoms; 1 or more constitutional symptom including headache, malaise, myalgia, sweats and/or chills or fatigue	21 days	defined as the time to the beginning of the first 24-hour period in which all influenza symptoms were rated as mild or less Secondary: Duration and severity of individual symptoms, incidence of secondary complications, quantity of viral shedding	group, and 71.5 hours (3.0 days) and 69.9 hours (2.9 days) in the 75 and 150 mg oseltamivir groups, respectively. Treatment with oseltamivir at either 75 or 150 mg BID resulted in statistically significant reductions (P<0.001 and P=0.006, respectively) in the area under the curve analysis of total symptom scores which reflects the severity and duration of illness. There were no differences between the two doses of oseltamivir with regard to effects. The 75 and 150 mg doses of oseltamivir reduced the severity of illness compared to placebo by 38 and 35%, respectively (P<0.001 for both). Secondary: Duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours (43% reduction) in the 75 mg group and to 40 hours (27% reduction) in the 150 mg group. The duration of myalgia was also reduced, from a median of 28 hours in the placebo group to 16 hours (42% reduction) in the 75 mg group and 19 hours (32% reduction) in the 150 mg group. After 24 hours of treatment, median viral titers had decreased by 1.2 logs in the placebo group vs 1.7 and 2.0 logs in the 75 and 150 mg oseltamivir groups, respectively. These differences were not statistically significant. Nausea and vomiting occurred more frequently in both the oseltamivir groups compared to the placebo group (P<0.001).
Nordstrom et al[50] Oseltamivir with a diagnosed influenza-like illness; Group1 vs oseltamivir with no diagnosis of influenza-like illness; Group 2	Cohort, RETRO Patients receiving oseltamivir or with a diagnosis of influenza-like illness	N=11,632 (Group 1) N=60,427 (Group 2) N=17,133 (Group 3) December 1, 1999 to	Primary: Diagnosis of pneumonia, hospitalization for any cause, dispensing of an antibiotic Secondary: Not reported	Primary: When comparing influenza-like illness with oseltamivir to influenza-like illness with no antivirals, the adjusted HR for pneumonia was 0.72 (95% CI, 0.60 to 0.86), for antibiotic dispensing the adjusted HR for pneumonia was 0.89 (95% CI, 0.86 to 0.93), and for hospitalization the adjusted HR for pneumonia was 0.74 (95% CI, 0.61 to 0.90). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs diagnosed with influenza-like illness with no antiviral therapy; Group 3		March 31, 2002		
Hayden et al[53] Zanamivir 6.4 mg by intranasal spray* plus 10 mg by inhalation BID for 5 days vs zanamivir 10 mg by inhalation plus placebo spray BID for 5 days vs placebo by both routes BID for 5 days	DB, RCT Adults with acute influenza of ≤48 hours duration	N=417 1994 to 1995 influenza season	Primary: Length of time to alleviation of all major symptoms Secondary: Not reported	Primary: Of 262 patients with confirmed influenza-virus infection (63% of all patients), the median length of time to the alleviation of all major symptoms was one day shorter (four vs five days) in the 88 patients given inhaled and intranasal zanamivir (P=0.02) and the 85 patients given inhaled zanamivir alone (P=0.05) than in the 89 patients given placebo. Among the infected patients who were febrile at enrollment and among those who began treatment within 30 hours after the onset of symptoms, the median time to the alleviation of major symptoms was four days in both zanamivir groups and seven days in the placebo group (P≤0.01). Secondary: Not reported
Monto et al[54] Zanamivir 10 mg inhaled BID for 5 days vs zanamivir 10 mg inhaled QID for 5 days vs placebo	DB, MC, PG, RCT Healthy persons ≥13 years of age who presented with symptoms of influenza ≤48 hours of duration	N=1,256 1995-1996 influenza season	Primary: Alleviation of all major symptoms Secondary: Nights of disturbed sleep, time to resumption of normal activities, use of symptom relief medications	Primary: In the overall population with or without influenza infection, zanamivir reduced the median number of days to alleviate all major symptoms by one day (P=0.012 two times daily vs placebo; P=0.014 QID vs placebo). The reduction was greater in patients treated within 30 hours of symptom onset, febrile at study entry, and in defined high-risk groups. Secondary: Zanamivir reduced nights of disturbed sleep (P=0.013, zanamivir QID vs placebo; P=0.026), time to resumption of normal activities (P=0.005, zanamivir QID vs placebo; P<0.001), and use of symptom relief medications (P<0.001, zanamivir QID vs placebo; P=0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Louie et al[55] Neuraminidase inhibitor therapy	RETRO Patients 0 to 17 years of age hospitalized in intensive care units with laboratory-confirmed influenza from April 3, 2009, through September 30, 2012	N=748 Duration varied	Primary: Mortality Secondary: Not reported	Primary: Of neuraminidase inhibitor-treated cases, 38 (6%) died compared with 11 (8%) of 131 untreated cases (OR, 0.67; 95% CI, 0.34 to 1.36). In a multivariate model that included receipt of mechanical ventilation and other factors associated with disease severity, the estimated risk of death was reduced in neuraminidase inhibitor-treated cases (OR, 0.36; 95% CI, 0.16 to 0.83). Treatment within 48 hours of illness onset was significantly associated with survival (P=0.04). Cases with neuraminidase inhibitor treatment initiated earlier in illness were less likely to die. Secondary: Not reported
Halloran et al[56] NI for post exposure prophylaxis vs placebo	MA Individuals >1 year of age who were household contacts of an individual diagnosed with influenza	N=3,902 14 days or more	Primary: Efficacy in preventing illness, reduction in infectiousness, reduction in pathogenicity Secondary: Not reported	Primary: Efficacy against illness was demonstrated with zanamivir (75%; 95% CI, 54 to 86) and oseltamivir (81%; 95% CI, 35 to 94). In zanamivir-treated patients, the effect on reducing infectiousness vs placebo treated patients was 19% (95% CI, -160 to 75) compared to 80% (95% CI, 43 to 93) for oseltamivir vs placebo. In reducing the pathogenicity, the efficacy of zanamivir was 52% (95% CI, 19 to 72) and 56% (95% CI, 14 to 77) in two studies, compared to 56% (95% CI, 10 to 73) and 79% (95% CI, 45 to 92) for two other studies with oseltamivir. Secondary: Not reported
Lin et al[57] Oseltamivir 75 mg BID for 5 days vs	OL, RCT Chinese patients at high risk initiating treatment within 48 hours after symptom onset	N=56 5 days of treatment, follow-up varied	Primary: Duration and severity of illness Secondary: Incidence of complications,	Primary: The duration and severity of influenza symptoms was significantly reduced in the oseltamivir group, by 36.8% (P=0.0479) and 43.1% (P=0.0002) respectively. Secondary: The duration of fever was significantly reduced in the oseltamivir group by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
symptomatic treatment			antibiotic use, hospitalizations	45.2% (P=0.0051), as was the proportion that returned to baseline health status within five days (11 vs 45%; P=0.0011). In the oseltamivir group, the incidence rates of complications (11 vs 45%; P=0.0053) and antibiotic use (37 vs 69%; P=0.0167) were significantly lower.
Kawai et al[58] Oseltamivir 75 mg for adults and 2 mg/kg for children <37.5 kg BID for 5 days to patients with either influenza A (Group 1) or influenza B (Group 2) vs amantadine 50 mg for adults and 1.5 to 2.5 mg/kg for children BID for 5 days to patients with influenza A (Group 3)	OL Patients diagnosed with influenza who received oseltamivir or amantadine therapy within 48 hours after symptom onset	N=2,163 5 days	Primary: Time from onset of symptoms to start of treatment, duration of fever, impact of age on outcome Secondary: Not reported	Primary: For all three groups, the duration of fever was significantly shorter in patients who received the medication within 12 hours after the onset of symptoms compared to >12 hours after the onset of symptoms (P<0.001). For patients in Group 2, the duration of fever was significantly longer when compared to Groups 1 and 3; however, there was no significant difference between Groups 1 and 3 (P<0.01 to <0.05). The duration of fever was significantly longer for patients in Groups 2 and 3 aged zero to six years when compared to those aged seven to 15 years and 16 to 64 years (P<0.001 to 0.01). The duration of fever of patients zero to six years in Group 1 was significantly shorter than for those same aged patients in Group 2 (P<0.01). For patients aged 16 to 64 years and >65 years, there was no significant difference between groups in duration of fever (P value not significant). Secondary: Not reported
Kawai et al[59] Oseltamivir 75 mg (for adults and for children who weighed 37.5 kg) or 2 mg/kg (for children who weighed <37.5 kg) BID for 5 days vs	MC, PRO Patients 5 years of age and older who reported to any of 27 clinics throughout Japan with influenza-like illness and received a diagnosis of influenza A or B based on the results	N=1,113 5 days	Primary: Duration of fever from onset, duration of fever after administration of first dose of oseltamivir or zanamivir, percentage of patients afebrile at	Primary: The duration of fever from its onset was significantly shorter for patients with influenza A treated with zanamivir compared to those treated with oseltamivir (31.8 and 35.5 hours, respectively; P<0.05). The duration of fever after starting zanamivir was significantly shorter compared to oseltamivir for influenza B (35.8 and 52.7 hours, respectively; P<0.001). No statistically significant differences in the percentage of patients afebrile at 24 or 48 hours after the first dose of drug were shown between zanamivir and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zanamivir 10 mg (for adults and children 5 years of age and older) inhaled BID for 5 days	of commercial antigen detection kits		24 and 48 hours after the first dose of zanamivir or oseltamivir, virus isolation before and after zanamivir therapy Secondary: Not reported	oseltamivir therapy in patients with influenza A (P value not reported). The percentage of patients afebrile at 24 or 48 hours after the first dose of drug was significantly higher in the zanamivir group compared to the oseltamivir group in patients with influenza B (P<0.001). No significant difference was observed in zanamivir patients with influenza A or influenza B (P value not reported). The percentage of patients afebrile 24 and 48 hours after starting oseltamivir was significantly higher for influenza A compared to influenza B (P<0.001). In patients five to 10 years of age, there was no significant difference in the re-isolation rate between influenza A (A/H3N2 or A/H1N1, 47.1%) and influenza B (36.1%). The re-isolation rate in patients >10 years of age and in all patients was significantly higher for influenza B (20.0 and 25.5%) than for influenza A (6.3 and 12.5%, respectively; P<0.01 and P<0.05, respectively). The re-isolation rate was significantly higher in patients five to 10 years of age than in patients >10 years of age for influenza A (P<0.001). Secondary: Not reported
Tuna et al[60] Oseltamivir vs zanamivir	RCT Patients diagnosed with influenza during the influenza season between October 1, 2009 and February 1, 2010	N=80 Duration varied	Primary: Efficacy and safety Secondary: Not reported	Primary: There was no significant difference in efficacy for the two drugs (P>0.05). Temperature normalization was significantly faster in patients taking zanamivir (P=0.0157). Drowsiness was the most frequent adverse event for both drugs (38% for the oseltamivir group, and 22% for the zanamivir group). Respiratory distress was observed in five patients in the zanamivir group, whereas it was not observed in patients in the oseltamivir group (P<0.05). One patient had to discontinue therapy in the zanamivir group due to respiratory distress. Secondary: Not reported
Hall et al[61]	DB, PC, RCT	N=91	Primary: Daily mean	Primary: On days two and three, the mean symptom score for patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rimantadine 6.6 mg/kg/day in two divided doses plus placebo QID vs acetaminophen 10 mg/kg QID plus placebo BID	Previously healthy children between 1 and 15 years of age with acute illness deemed by their physician's to be compatible with influenza A	7 days	symptom score, reduction in fever, mean score for severity of illness, daily percentage of children shedding influenza virus from their nasal lavage specimens, percentage of resistant isolates, mean inhibitory concentration Secondary: Not reported	rimantadine was significantly less (P=0.05, P<0.01 respectively). Thereafter, the mean scores were not significantly different. Eighty-nine percent of observed reduction in fever occurred in the first 24 hours in the rimantadine group compared to 60% in the acetaminophen group. The mean peak temperature in the rimantadine group on day three was 37.3°C vs 37.8°C in the acetaminophen group (P<0.04). Of those in the rimantadine group, 86% had peak temperatures <38°C in comparison to 66% in the acetaminophen group. The mean score for severity of illness was significantly less on day four (P<0.04) for the rimantadine treated patients. The proportion of children shedding the influenza virus on the second day of therapy was significantly reduced in the rimantadine group on day two (P=0.006). However, on days five, six, and seven, the percentage of patients shedding the virus in the rimantadine group increased in contrast to a continued decrease in the acetaminophen group; the difference was significant on day six (P=0.05) and seven (P=0.02). An initial decrease in quantity of virus shed in the nasal lavage specimens in the rimantadine group was observed on day two (P=0.03), followed by a significant increase in comparison to acetaminophen treated patients on day seven (P=0.03). The duration of viral shedding in those receiving rimantadine was 5.6 days compared to 4.5 days for those receiving acetaminophen (P<0.04). By day seven, 45.4% of those who received rimantadine compared to 12.5% of those treated with acetaminophen were shedding virus that had developed resistance to rimantadine during the course of therapy (P<0.03). Twenty-seven percent of the rimantadine patients were shown to have resistant isolates in comparison to 6% of patients in the acetaminophen group (P<0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean inhibitory concentration of rimantadine increased with time in the rimantadine group (P=0.002) but not in the acetaminophen group. Secondary: Not reported
Duval et al[62] Oseltamivir 75 mg BID plus zanamivir 10 mg by inhalation BID (OZ) vs oseltamivir 75 mg BID plus inhaled placebo (O) vs zanamivir 10 mg by inhalation BID plus oral placebo (Z)	DB, PC, RCT French adults 18 years of age and older who consulted their general practitioner within 36 hours of influenza symptoms, with a temperature ≥38°C, one or more respiratory symptoms, one or more general symptoms, and a positive nasal rapid test for influenza A	N=541 7 days	Primary: Proportion of patients with nasal influenza reverse transcription-PCR below 200 copies genome equivalent/µL at day two Secondary: Decrease of log10 viral load between days zero and two, time to resolution of illness, number of patients with alleviation of symptoms at the end of treatment (day five), symptoms score at the end of treatment, incidence of secondary complications of influenza, occurrence of adverse events in	Primary: The proportion of patients with a reverse transcriptase-PCR, 200 copies genome equivalent/µL on day two of treatment was 52.6% for OZ, 62.5% for O (P=0.055, for the OZ vs O comparison, treatment effect comparison, 29.9%; 95% CI, 219.9 to 0.2), and 40.5% for Z (P=0.020, for the OZ vs Z comparison; treatment effect comparison, 12.1%; 95% CI, 2.02 to 22.3). The O vs Z comparison was 22%; 95% CI, 12.1 to 32.0. Secondary: The day two to day zero decrease of log10 viral load was 2.14 log10 copies genome equivalent/µL for OZ, 2.49 log10 copies genome equivalent/µL for O, (P=0.060 for the OZ vs O comparison; treatment effect comparison, 20.35; 95% CI, 20.8 to 0.07), and 1.68 log10 copies genome equivalent/mL for Z (P=0.016 for the OZ vs Z comparison; treatment effect comparison, 0.46; 95% CI, 0.03 to 0.9). The median time to resolution of illness was 3.5 days for OZ, 3.0 days for O (P=0.015 for the OZ vs O comparison; treatment effect comparison, 0.5%; 95% CI, 0.0 to 1.5), and 4.0 days for Z (P=0.78 for the OZ vs Z comparison; treatment effect comparison, 20.5; 95% CI, 21.0 to 0.5). The O vs Z comparison was -1.0; 95% CI, -1.5 to -0.5. The number of patients with alleviation of symptoms at the end of treatment (day five) was 26 (13.5%) for OZ, 15 (8.5%) for O (P=0.014 for the OZ vs O comparison; treatment effect comparison, 5%; 95% CI, -1.3 to 11.4), and 23 (13.3%) for Z (P=0.93 for the OZ vs Z comparison; treatment effect comparison, 1.0; 95% CI, -6.7 to 7.2). The O vs Z comparison was 11.5%; 95% CI, 1.7 to 21.3. The median symptoms score at day five (end of treatment) was three for OZ, two for O (P=0.013 for the OZ vs O comparison; treatment effect comparison,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			all participants having received at least one dose	1; 95% CI, 0.0 to 1.0), and three for Z (P=0.93 for the OZ vs Z comparison; treatment effect comparison, 0.0; 95% CI, 21.0 to 0.0). The O vs Z comparison was -1.0; 95% CI, -2.0 to -1.0. The percentage of patients with clinical event during treatment was 26 (13.5%) for OZ, 15 (8.5%) for O (P=0.14 for the OZ vs O comparison; treatment effect comparison, 5.0%; 95% CI, 21.3 to 11.4, and 23 (13.3%) for Z (P=1.00 for the OZ vs Z comparison; treatment effect, 0.3%; 95% CI, 26.7 to 7.2). The O vs Z comparison was -4.8%; 95% CI, -11.2 to 1.6. Nausea and/or vomiting tended to be more frequent in the combination arm (OZ, 13; O, 4; and Z, 5 patients, respectively).
Hsu et al[63] Antiviral drugs (amantadine, oseltamivir, rimantadine, zanamivir) vs placebo	MA Patients receiving any of the antiviral drugs for the treatment of laboratory-confirmed influenza or influenza-like illness (not confirmed)	N=Not reported Duration not reported	Primary: Mortality, hospitalization, ICU admission, mechanical ventilation and respiratory failure, duration of hospitalization, duration of signs and symptoms, time to return to normal activity, complications, critical adverse events (major psychotic disorders, encephalitis, stroke, or seizure), important adverse events (pain in extremities, clonic twitching, body	Primary: There was a reduction in mortality with oseltamivir treatment compared to no antiviral therapy (OR, 0.23; 95% CI, 0.13 to 0.43). The overall grade for the quality of evidence was low. A pooled estimate of unadjusted effects from nine studies resulted in a more modest reduction in mortality (OR, 0.51; 95% CI, 0.23 to 1.14). Treatment with oseltamivir reduced hospitalizations in outpatients compared to patients treated with placebo (OR, 0.75; 95% CI, 0.66 to 0.89). Oseltamivir reduces the duration of fever by approximately 33 hours (95% CI, 21 to 45 hours) from onset of symptoms compared to no antiviral therapy (SMD, -0.91; 95% CI, -1.25 to -0.57). Oseltamivir may be associated with fewer adverse events compared to no antiviral therapy (RR, 0.76; 95% CI, 0.70 to 0.81). At six months, one study found a reduction in risk for stroke and transient ischemic attacks in patients <65 years who received oseltamivir (HR, 0.66; 95% CI, 0.56 to 0.77). Oseltamivir was not associated with fewer complications, such as pneumonia (OR, 0.83; 95% CI, 0.59 to 1.16) or any recurrent cardiovascular outcome (OR, 0.58; 95% CI, 0.31 to 1.10); however, there was a reduction in otitis media (OR, 0.75; 95% CI, 0.64 to 0.87). The incidence of resistance to oseltamivir treatment across five studies was 30

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			weakness, or dermatologic changes), influenza viral shedding and emergence of antiviral resistance Secondary: Not reported	per 1000 patients (95% CI, 10 to 60) and influenza virus was detectable in 330 per 1000 patients (95% CI, 280 to 370) approximately five days after treatment with oseltamivir. No study compared the persistence of influenza virus between patients who received oseltamivir and those who did not. There was no significant reduction in hospitalization following inhaled zanamivir treatment compared to those who receive no antiviral therapy (OR, 0.66; 95% CI, 0.37 to 1.18). Zanamivir reduced the duration of symptoms by approximately 23 hours (95% CI, 17 to 28) on the basis of a large SMD (-0.94; 9% CI, -1.21 to -0.66). There was no increased risk of including otitis media (OR, 1.19; 95% CI, 0.67 to 2.14), respiratory disease (OR, 1.17; 95% CI, 0.98 to 1.39). The combined results of five Japanese studies in patients with confirmed influenza suggest that inhaled zanamivir may be associated with slightly shorter symptom duration than oseltamivir (difference, 7 hours; 95% CI, 2 to 12). There was no statistically significant difference between oseltamivir and inhaled zanamivir with regard to hospitalizations (OR, 1.40; 95% CI, 0.45 to 4.35) or ICU admissions (OR, 0.58; 95% CI, 0.16 to 2.18) in pregnant women. The results of another study demonstrated no statistically significant difference in influenza viral detection after five days between the treatments (OR, 3.05; 95% CI, 0.78 to 11.96). The results of one study reported that amantadine may reduce mortality (OR, 0.04; 95% CI, 0.00 to 0.73) and pneumonia (OR, 0.76; CI, 0.38 to 1.53) compared to no antiviral therapy; however, time to alleviation of symptoms did not significantly between treatments. No studies that compared rimantadine with no antiviral therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Influenza Treatment and Prophylaxis				
Jefferson et al[64] NI as prophylaxis and/or treatment for influenza or influenza like illness vs placebo	MA Individuals with known pre-existing chronic pathology known to aggravate the course of influenza	N=1,014 patients received a NI 22 to 49 days	Primary: Efficacy (distribution and/or severity of influenza), viral load, adverse events Secondary: Not reported	Primary: NIs did not demonstrate an effect against influenza like illness when used as prophylaxis when compared to placebo (RR, 1.28; 95% CI, 0.45 to 3.66 for oseltamivir and RR, 1.51; 95% CI, 0.77 to 2.95 for zanamivir). Against symptomatic influenza, the efficacy of oseltamivir was 61% (RR, 0.39; 95% CI, 0.18 to 0.85) at the 75 mg dose and 73% (RR, 0.27; 95% CI, 0.11 to 0.67) at the 150 mg dose. Zanamivir was calculated to be 62% efficacious (RR, 0.38; 95% CI, 0.17 to 0.85). There was no significant effect from either NI on asymptomatic influenza (P value not reported). Nausea was associated with oseltamivir (OR, 1.79; 95% CI, 1.10 to 2.93). In the treatment of post-exposure prophylaxis, oseltamivir was found to have an efficacy rate of 58.5% (95% CI, 15.6 to 79.6) for households and 68.0% (95% CI, 34.9 to 84.2) to 89.0% in contacts of index cases; similar findings were reported for zanamivir (P value not reported). Results for alleviation of influenza symptoms favored the treatment groups (HR, 1.33; 95% CI, 1.29 to 1.37 for zanamivir and HR, 1.30; 95% CI, 1.13 to 1.50 for oseltamivir). Both NIs significantly diminished nasal titers (no P value reported). The use of oseltamivir was associated with lower respiratory tract complications (OR, 0.32; 95% CI, 0.18 to 0.57). Secondary: Not reported
Turner et al[65] NI as prophylaxis and/or treatment for influenza	MA Children, healthy adults, and adults at	N=29 studies Duration varied up to	Primary: Median duration of symptoms, risk of infection	Primary: For influenza-positive patients, treatment with oseltamivir reduced the median duration of symptoms in the influenza positive group by 1.38 days (95% CI, 0.80 to 1.96) for otherwise healthy adults; by 0.50 days (95% CI, -0.96 to 1.88)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	high risk	28 days	Secondary: Not reported	for the high-risk population, and by 1.50 days (95% CI, 0.8 to 2.2) for the group of children. Prophylaxis with oseltamivir resulted in a relative risk reduction of 75 to 90% depending on the strategy used and the patient population studied (no P value reported). For influenza-positive patients, treatment with zanamivir reduced the median duration of symptoms in the influenza positive group by 1.26 days (95% CI, 0.59 to 1.93) for otherwise healthy adults; by 1.99 days (95% CI, 0.90 to 3.08) for the high-risk population, and by 1.30 days (95% CI, 0.3 to 2.0) for the group of children. Prophylaxis with zanamivir resulted in a relative-risk reduction of 70 to 90% depending on the strategy used and the patient population studied (P value not reported). Secondary: Not reported
Cooper et al[66] NI as prophylaxis and/or treatment for influenza vs placebo or standard care	MA Children, healthy adults, and adults at high risk	N=>1,000 (exact number not specified) 21 to 28 days	Primary: Duration of symptoms in days Secondary: Not reported	Primary: In the intent-to treat-population with zanamivir, the median duration of symptoms in days was reduced by 1.0 (95% CI, 0.5 to 1.5) in the treatment of children, 0.8 (95% CI, 0.3 to 1.3) in otherwise healthy individuals, and 0.9 (95% CI, -0.1 to 1.9) for high risk individuals. In the intent-to-treat population with oseltamivir, the median duration of symptoms in days was reduced by 0.9 (95% CI, 0.3 to 1.5) in the treatment of children, 0.9 (95% CI, 0.3 to 1.4) in otherwise healthy individuals, and 0.4 (95% CI, -0.7 to 1.4) for high risk individuals. A relative reduction of 70 to 90% in the odds of developing influenza was associated with the prophylactic use of zanamivir or oseltamivir (P values not reported). Some studies did not present the vaccination status of the individuals; for the ones that did, the percentage of patients vaccinated ranged from 0 to 80%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Jefferson et al[67] Amantadine, rimantadine, or NI as prophylaxis and/or treatment for influenza vs placebo, no intervention, or symptomatic medication	MA Otherwise healthy individuals 16 to 65 years of age	N=52 trials Duration varied	Primary: Prophylactic efficacy, duration of nasal shedding, time to alleviate symptoms, adverse events, lower respiratory tract complications Secondary: Not reported	Primary: For the prophylaxis of influenza A and influenza-like illness amantadine prevented 61% (95% CI, 35 to 76) and 25% (95% CI, 13 to 36) of cases respectively. The use of amantadine was associated with nausea (OR, 2.56; 95% CI, 1.37 to 4.79), insomnia and hallucinations (2.54; 95% CI, 1.50 to 4.31). The duration of fever in days was significantly shortened with amantadine compared to placebo (0.99; 95% CI, -1.26 to -0.71), in comparison with nasal shedding of influenza A, no significant difference was seen (0.93; 95% CI, 0.71 to 1.21). Compared to placebo when used for prophylaxis, NI had no significant effect on influenza-like illness (1.28; 95% CI, 0.45 to 3.66 for oseltamivir 75 mg a day and 1.51; 95% CI, 0.77 to 2.95 for zanamivir 10 mg a day). Against symptomatic influenza, oseltamivir was 61 or 73% (75 and 150 mg doses) effective, while zanamivir was 62% efficacious (no P value reported). Nausea was associated with the use of oseltamivir (OR, 1.79; 95% CI, 1.10 to 2.93). The protective efficacy of oseltamivir was 58.8% from household contacts and from 68.0 to 89.0% in contacts of index cases. Compared to placebo the HRs for the time-to-alleviate symptoms were 1.33 (95% CI, 1.29 to 1.37) for zanamivir and 1.30 (95% CI, 1.13 to 1.50) for oseltamivir, when the medications were started within 48 hours of onset of symptoms. In preventing lower respiratory tract complications in influenza cases, oseltamivir 150 mg QD was judged to be effective (OR, 0.32; 95% CI, 0.18 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.57). Secondary: Not reported
Wang et al[68] Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir and laninamivir*) vs placebo or other antiviral drugs	SR Healthy and at-risk children <12 years of age	N=2,356 Duration not specified	Primary: Time to resolution of illness, return to normal activity or school, resolution of symptoms, complications, discontinuation/ withdrawal and systemic events Secondary: Symptom scores, highest daily temperature, sleep disturbance, rescue medication, antibiotic use and hospital admissions	Primary: Time to resolution of illness (i.e. resolution of symptoms and return to usual activities) In one study, treatment with oseltamivir reduced the median duration of illness by 1.5 days (26%, P<0.0001), from 5.7 to 4.2 days in the ITTI population. A small but significant reduction of 0.88 days was seen in the ITT population (a 17% reduction, from 5.3 to 4.4 days, P=0.0002). In a study evaluating oseltamivir in children with asthma, there was no significant reduction in the median duration of illness compared to placebo (from 5.60 to 5.16 days, P=0.54) in the ITTI population. Time to resolution of influenza symptoms Zanamivir treatment reduced the median time to the resolution of symptoms by 1.25 days (from 5.25 to 4 days; P<0.001) in the ITTI population, with a smaller improvement of 0.5 days (from 5.0 to 4.5 days; P=0.001) in the ITT population. In another study, zanamivir treatment reduced the median time to resolution of symptoms by 0.5 days (from 5.5 to 5.0 days; P<0.0377) in the ITT population. Treatment with oseltamivir significantly reduced the median time to the resolution of all symptoms by 36 hours (from 100 to 63 hours; P<0.0001) in the ITTI population. In two studies, treatment with oseltamivir did not significantly reduce in the median time to alleviation of all symptoms (115.6 to 90.4 hours; P=0.1197) in the ITTI population. Results from one study reported that oseltamivir treatment reduced the median duration of symptoms by 2.8 days in children with laboratory-confirmed influenza A or B (P<0.001). Treatment with laninamivir octanoate 20 mg reduced duration of influenza symptoms by 31 hours compared to oseltamivir in children with influenza diagnosed on rapid near-patient testing (36%, P=0.009); however, no statistically significant difference was reported with laninamivir octanoate 40mg in these children (P=0.059).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Time to return to normal activities Zanamivir treatment reduced the median time to return to normal activity by one day in both the ITTI (P=0.022) and the ITT populations (P=0.019). After the five-day observation period, 36.0% of participants who received zanamivir and 28.1% of the placebo group returned to school in the ITT population (P=0.19). Treatment with oseltamivir reduced the median time to return to normal activity by 1.9 days (40%; P<0.0001) in the ITTI population. No data were available for the ITT population. There was a nonsignificant trend towards benefit with oseltamivir in asthmatic children with laboratory-confirmed influenza, with a reduction in median time to return to normal activity of 12.6 hours (11%; P=0.46). There was no data available for the ITT population. Children treated with oseltamivir returned to daycare two days sooner than children in the placebo (P=0.01). Secondary: Other secondary outcome measures Zanamivir reduced time to resolution of illness (no further use of relief medication) by 1.5 days in the ITTI population (from 6.5 to 5.0 days, P<0.001) and 1.0 days in the ITT population (from 6.0 to 5.0 days, P=0.002). There was no significant difference between patients treated with zanamivir or placebo with regard to the time to resolution of cough (P=0.1960). Oseltamivir treatment reduced the median time to resolution of fever by 1.0 days (from 2.8 days to 1.8 days; P<0.0001), time to return to normal health and activity by 0.53 days (from 4.75 to 4.23 days; P=0.4555) and time to alleviation of all symptoms by 1.05 days (from 4.82 to 3.77 days; P=0.1197). The mean number of doses of antipyretics and/or analgesics was significantly decreased in children with laboratory-confirmed influenza treated with oseltamivir (P=0.01) in children with influenza A; however, no difference was observed in children with influenza B (P=0.88). No children in the ITTI population were diagnosed with pneumonia or hospitalized during the treatment period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Treatment with oseltamivir was associated with a small reduction in the incidence of otitis media in children aged one to five years with laboratory-confirmed influenza (RD, -0.14; 95% CI, -0.24 to -0.04). Results of one trial with zanamivir did not demonstrate any difference in the incidence of otitis media between children treated with zanamivir or placebo. Overall, treatment with neuraminidase inhibitors did not significantly reduce antibiotic use (RD, -0.07; 95% CI, -0.15 to 0.01).
Jefferson et al[69] Oral or inhaled amantadine or oral rimantadine as prophylaxis and/or treatment for influenza vs placebo, standard medications (aspirin and other antipyretic or anti-inflammatory medications), other antiviral medications or no intervention	MA Otherwise healthy individuals aged 14 to 60	N=36 trials Duration varied	Primary: Numbers of influenza cases, severity of cases, rate of death, length of nasal shedding, persistence of virus in the upper airways, adverse effects Secondary: Not reported	Primary: For the comparison of prophylaxis of influenza and influenza-like illness, amantadine prevented 61% (95% CI, 35 to 76) and 25% (95% CI, 13 to 36) of the cases respectively. The duration of fever was significantly shortened by amantadine compared to placebo (0.99 days; 95% CI, 0.71 to 1.26). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR, 0.96; 95% CI, 0.72 to 1.27). Amantadine use was associated with gastrointestinal symptoms (OR, 2.56; 95% CI, 1.37 to 4.79), insomnia and hallucinations (OR, 2.54; 95% CI, 1.50 to 4.31), and withdrawals from the trials because of adverse events (OR, 2.54; 95% CI, 1.60 to 4.06) in the prophylaxis trials. There was no evidence that amantadine use was associated with increased adverse event rates compared to placebo use in treatment trials. For the prophylaxis of influenza and influenza-like illness, rimantadine was not effective against either influenza (RR, 0.28; 95% CI, 0.08 to 1.08) or influenza-like-illness (RR, 0.65; 95% CI, 0.35 to 1.20). The duration of fever was significantly shortened by rimantadine compared to placebo (1.24 days; 95% CI, -0.76 to -1.71). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR, 0.67; 95% CI, 0.22 to 2.07). Rimantadine use was associated with experiencing all adverse events more than placebo recipients (OR, 1.96; 95% CI, 1.19 to 3.22).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the comparison of amantadine vs rimantadine for prophylaxis of influenza or influenza-like illness, there was no difference in efficacy (RR, 0.88, 95% CI, 0.57 to 1.35). There was no difference in efficacy comparing amantadine to rimantadine for treatment. The comparison of amantadine to rimantadine confirmed that central nervous system adverse events (OR, 3.11; 95% CI, 1.67 to 5.78) and withdrawal from trials (OR, 2.49; 95% CI, 1.26 to 4.93) were significantly more frequent among amantadine recipients. The effects of oral or inhaled amantadine on the shedding of influenza A viruses were not significant (RR, 0.93; 95% CI, 0.71 to 1.21). There was no difference in the duration of fever in the comparison of amantadine against standard medications (weighted mean difference, 0.25; 95% CI, -0.37 to 0.87). In the comparison of inhaled amantadine vs placebo, amantadine was no more effective than placebo in bringing down the respiratory or constitutional symptom score (weighted mean difference, 1.0; 95% CI, 3.64 to 1.64 and -2.0; 95% CI, 16.9 to 12.9 respectively). Secondary: Not reported
Alves Galvao et al[70] Amantadine and/or rimantadine vs placebo, control drugs or no intervention	SR Pediatric and elderly patients requiring prophylaxis and/or treatment for influenza A	N=2,494 Duration varied (follow up ranged from 8 to 120 days)	Primary: Response to treatment, cases of influenza, cases of adverse events in pediatric and elderly patients Secondary:	Primary: Amantadine and rimantadine vs control (placebo and acetaminophen) in the treatment of influenza A in pediatric patients There was a protective effect of amantadine and rimantadine in the occurrence of fever on day three of antiviral treatment, when trials using both antivirals were combined (RR, 0.39; 95% CI, 0.20 to 0.79). The number of patients needed to treat to prevent one case of fever on day three of treatment was 5.88 (95% CI, 4.55 to 16.67). A protective effect of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	rimantadine for this outcome was also verified (RR, 0.36; 95% CI, 0.14 to 0.91). The number of patients needed to treat to prevent one case of fever on day three of treatment was 4.12 (95% CI, 3.03 to 33.33). No protective effect of amantadine was observed in the occurrence of fever on day three of treatment (RR, 0.37; 95% CI, 0.08 to 1.75). No protective effect of rimantadine was observed regarding the occurrence of any of the following outcomes: cases of pain on movement and visual distortion on day five (RR, 0.58; 95% CI, 0.10 to 3.24), conjunctivitis on day five (RR, 0.17; 95% CI, 0.01 to 3.49), malaise on day six (RR, 1.04; 95% CI, 0.63 to 1.70) and cough on day seven (RR, 0.83; 95% CI, 0.63 to 1.10). No trials reported the use of amantadine for these outcomes. Amantadine and rimantadine vs control (placebo and specific treatment) in the prophylaxis of influenza A in pediatric patients A protective effect of amantadine was demonstrated (RR, 0.11; 95% CI, 0.04 to 0.30). No protective effect of rimantadine was demonstrated in the prophylaxis of cases of influenza (RR, 0.49; 95% CI, 0.21 to 1.15). Adverse events of amantadine and rimantadine vs control (placebo and acetaminophen) in pediatric patients Amantadine was not related to a higher risk of the following adverse events: diarrhea (RR, 0.79; 95% CI, 0.42 to 1.47), exanthema (RR, 0.69; 95% CI, 0.21 to 2.34), muscular limb pain (RR, 0.85; 95% CI, 0.46 to 1.59), headache (RR, 0.73; 95% CI, 0.52 to 1.03) and stimulation and insomnia (RR, 0.46; 95% CI, 0.12 to 1.74). Amantadine was not associated with dizziness (RR, 6.63; 95% CI, 0.32 to 137.33) and dyspnea (RR, 0.37; 95% CI, 0.02 to 9.02). Rimantadine was not related to a higher risk of any of the following adverse events: central nervous system symptoms (RR, 0.23; 95% CI, 0.01 to 4.70), change in behavior (RR, 0.23; 95% CI, 0.01 to 4.70), diarrhea (RR, 0.36; 95% CI, 0.02 to 8.41), dizziness (RR, 3.21; 95% CI, 0.14 to 75.68), gastrointestinal manifestations (RR, 1.17; 95% CI, 0.08 to 18.05), hyperactivity (RR, 0.36; 95% CI, 0.02 to 8.41), tinnitus (RR, 3.21; 95% CI, 0.14 to 75.68) and cerebellar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ataxia (RR, 2.61; 95% CI, 0.11 to 61.80). Rimantadine was not associated with nausea and vomiting (RR, 0.96; 95% CI, 0.10 to 9.01). Use of different doses of amantadine and rimantadine for prophylaxis and treatment of influenza in pediatric patients, adverse events related to different doses of amantadine and rimantadine in pediatric patients and amantadine and rimantadine vs other antivirals in pediatric patients There were no trials conducted in pediatric patients for these comparisons. Amantadine and rimantadine vs control in the treatment of influenza A in elderly patients There was no trial selected for this comparison. Amantadine and rimantadine vs control (placebo and zanamivir) in the prophylaxis of influenza A in elderly patients No protective effect of rimantadine was observed regarding the prophylaxis of influenza in elderly patients (RR, 0.74; 95% CI, 0.13 to 4.07). There was no amantadine trial selected for this comparison. Adverse events of amantadine and rimantadine vs control (placebo) in elderly patients No effect of rimantadine was demonstrated regarding any of the following adverse events: stimulation and insomnia (RR, 1.61; 95% CI, 0.43 to 6.02), confusion (RR, 0.79; 95% CI, 0.40 to 1.56), fatigue (RR, 0.81; 95% CI, 0.41 to 1.60), vomiting (RR, 0.99; 95% CI, 0.38 to 2.60), headache (RR, 0.83; 95% CI, 0.21 to 3.38), impaired concentration (RR, 0.50; 95% CI, 0.10 to 2.41), rash or allergic reaction (RR, 3.53; 95% CI, 0.18 to 67.28), seizures or clonic twitching (RR, 2.00; 95% CI, 0.23 to 17.54), dry mouth (RR, 0.70; 95% CI, 0.23 to 2.12), dizziness (RR, 0.94; 95% CI, 0.15 to 5.97) and anxiety (RR, 2.83; 95% CI, 0.92 to 8.74). There was no amantadine trial selected for this comparison. Use of different doses of amantadine and rimantadine for prophylaxis and treatment of influenza A in elderly patients A reduced dose of rimantadine (100 mg/day) was comparable to the full dose (200 mg/day) for prophylaxis (RR, 0.93; 95% CI, 0.21 to 4.20). There was no selected trial using different doses of rimantadine in elderly patients, nor any

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				selected trial comparing different doses amantadine for prophylaxis and treatment of influenza A in elderly patients. Adverse events related to different doses of amantadine and rimantadine in elderly patients There was no protective effect of a reduced dose of rimantadine in the occurrence of the following adverse events: confusion (RR, 0.83; 95% CI, 0.41 to 1.65), depression (RR, 0.44; 95% CI, 0.12 to 1.65), impaired concentration (RR, 0.68; 95% CI, 0.11 to 3.98), insomnia or sleeplessness (RR, 1.02; 95% CI, 0.26 to 3.97), loss of appetite (RR, 0.62; 95% CI, 0.27 to 1.46), rash or allergic reaction (RR, 0.34; 95% CI, 0.04 to 3.21), seizures or clonic twitching (RR, 0.11; 95% CI, 0.01 to 2.07), dry mouth (RR, 1.16; 95% CI, 0.43 to 3.11), fatigue or drowsiness (RR, 1.14; 95% CI, 0.45 to 2.87), headache (RR, 1.02; 95% CI, 0.30 to 3.42) and body weakness or debility (RR, 0.91; 95% CI, 0.38 to 2.18). There was no amantadine trial selected for this comparison. Amantadine and rimantadine vs other antivirals in elderly patients When rimantadine was compared to zanamivir it was demonstrated that zanamivir prevented influenza A more effectively than rimantadine. There was no amantadine trial selected for this comparison. Secondary: Not reported
Younkin et al[71] Amantadine 100 mg orally QD for 5 days vs amantadine 200 mg orally QD for 5 days vs aspirin 3.25 g orally QD	DB, PRO College students, 17 to 20 years of age, with symptoms <48 hours duration	N=48 7 days	Primary: Symptomatic improvement; symptoms measured included upper respiratory symptoms (earache or obstruction, nasal discharge or obstruction, sore throat,	Primary: The aspirin treatment group defervesced more rapidly, in 10.3 vs 21.5 hours for the amantadine 100 mg group and 23.6 hours for the amantadine 200 mg group; P<0.01. When mean daily symptom scores were tabulated, the volunteers receiving 100 mg of amantadine daily had significantly lower values at 48 and 72 hours than did the volunteers receiving aspirin (P<0.01). Although the group who received 200 mg of amantadine had substantially lower overall symptom scores than the aspirin treatment group, this difference did not achieve statistical significance (0.05<P<0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 5 days			hoarseness), lower respiratory symptoms (chest pain, cough), and systemic symptoms (feverishness, chills, myalgias, malaise, headache, and anorexia) Secondary: Adverse events	Bothersome adverse events resulted in discontinuation of therapy by 35% of patients in the aspirin group but only 3% of patients in the amantadine group (P<0.05).
Parkinson's Disease				
Crosby et al[72] Amantadine monotherapy or adjuvant therapy for idiopathic Parkinson's disease vs placebo	MA Patients of all ages with a clinical diagnosis of idiopathic Parkinson's disease	N=215 Duration varied	Primary: Parkinson's disease motor impairment rating scales, tests of motor impairments Secondary: Not reported	Primary: Four of the six trials were not eligible for efficacy analysis. Three trials were XO trials that did not present data from the first arm. One of those three trials also only presented data from the amantadine arm. The 4th trial compromised randomization and did not analyze the results on an intention to treat basis. Of the remaining two trials, one found that amantadine treated patients were 15.0 points better in Parkinsonian symptoms severity scale after nine weeks of treatment (average baseline score of 21.4). The trial also found that patients treated with amantadine scored 28.1 points better (average baseline score of 38.3) on the activity impairment scale compared to placebo. The remaining trial did not provide standard deviations or baseline scores so the study was unable to be analyzed. Secondary: Not reported
Drug-Induced Extrapyramidal Reactions				
Verhagen Metman et al[73] Amantadine 100 mg for 3 weeks	DB, PC, XO Patients with advanced Parkinson's	N=18 3 weeks	Primary: Parkinsonian symptoms and choreiform	Primary: In the 14 patients completing the trial, amantadine reduced dyskinesia severity by 60% compared to placebo (P=0.001), without altering the antiparkinsonian effect of levodopa.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo The number of capsules was titrated up to 1 capsule TID or QID over a period of 4 to 6 days depending on age, renal function, and tolerance.	disease complicated by motor fluctuations and peak-levodopa-dose (also known as "on") dyskinesia; mean age was 60 years and mean symptom duration was 13 years		dyskinesias as observed during the last two hours of a seven-hour levodopa infusion, symptoms were scored using an abbreviated Unified Parkinson's Disease Rating Scale and a modified Abnormal Involuntary Movement Scale Secondary: Dyskinesias scored by a neurologist who observed the patients via study videotapes	Motor fluctuations occurring with patients' regular oral levodopa regimen also improved according to Unified Parkinson's Disease Rating Scale and patient-kept diaries. Parkinsonian symptoms measured during the levodopa infusion were similar with the addition of amantadine to the symptoms observed with placebo. Although four patients had to discontinue because of adverse events from active treatment, including confusion, hallucinations, palpitations, and nausea, all 14 patients completing the study requested that amantadine be added to their usual antiparkinsonian regimen. Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 49% with amantadine (3.6±0.6) compared to placebo (7.0±0.9; P<0.01).
Metman et al[74] Amantadine 100 mg capsule, TID or QID vs placebo All other antiparkinsonian medications were continued until the night	DB, PC Patients from the above study on the effects of amantadine on levodopa-induced motor complications, evaluated 1 year later; 17 out of 18 of the original subjects participated; 13 of 17 had stayed on oral	N=17 1 year and 7 to 10 days of supervised adminis-tration	Primary: Parkinsonian symptoms and dyskinesia severity evaluated after a seven-hour levodopa infusion, symptoms were scored using standard rating scales and compared to	Primary: One year after initiation of amantadine co-therapy, its anti-dyskinetic effect was similar in magnitude (56% reduction in dyskinesia; P<0.01) as compared to the placebo arm of the preceding trial (the reduction with amantadine one year earlier had been 60%). Motor complications occurring with the patients' regular oral levodopa regimen also remained improved according to the Unified Parkinson's Disease Rating Scale-IV. The beneficial effects of amantadine on motor response complications were maintained for at least one year after treatment initiation.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before levodopa infusion was administered.	amantadine throughout the year		results from one year earlier Secondary: Dyskinesias scored by a neurologist via watching a videotape	Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 43% with amantadine (3.6±0.6) compared to placebo (6.3±0.8; P<0.05).
Thomas et al[75] Amantadine 300 mg/day vs placebo	DB, RCT Patients with severe Parkinson's disease and peak dose or diphasic dyskinesia with or without pain levodopa-induced dyskinesia; all patients had also been receiving dopamine agonists as part of their treatment	N=40 9 months	Primary: Dyskinesia measured by the Unified Parkinson's Disease Rating Scale, the Dyskinesias Rating Scale and an Investigator Global Assessment of dyskinesia; change in dyskinesia from study initiation to study end Secondary: Scale score changes and the durations of the "on" and "off" states (periods when levodopa is exerting its effect vs periods when	Primary: After 15 days of amantadine treatment, there was a reduction by 45% in the Dyskinesias Rating Scale total dyskinesia scores (P<0.001). Unified Parkinson's Disease Rating Scale scores also decreased significantly with amantadine as compared to placebo (P<0.01). Within the next eight months, all patients in the amantadine group withdrew from the study as dyskinesia increased according to all scales. By the time of withdrawal there were no significant changes in dyskinesia from study baseline. Three patients in the amantadine group withdrew because of adverse events (tachycardia, psychosis or livedo reticularis). Eighteen patients in the placebo group withdrew from the study within three months because dyskinesia had not improved or had gotten worse. The other two patients in the placebo group withdrew because of adverse events. Secondary: Unified Parkinson's Disease Rating Scale I-III scores and "off" time were reduced and "on" time was increased in the amantadine group, but this improvement did not persist over the course of the study. Only the initial Unified Parkinson's Disease Rating Scale score reductions were statistically significant vs baseline and placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			levodopa effect has worn off)	
Wolf et al[76] Amantadine, individual daily dose vs placebo	DB, PC, PG, RCT Adult patients with a diagnosis of Parkinson's disease who had developed levodopa-induced dyskinesia and who had been receiving amantadine for ≥1 year	N=32 3 weeks	Primary: Change from baseline of dyskinesia duration and severity assessed by Unified Parkinson's Disease Rating Scale IV items 32 and 33 Secondary: Daily duration of "on" time with troublesome dyskinesias, "on" time with non-troublesome dyskinesias and "on" time without dyskinesias and total daily "off" time as assessed in 24 hour self-scoring diaries; motor function during "on" periods; safety	Primary: Among the intent to treat population, placebo was associated with a significant increase in dyskinesia disability and duration after three weeks compared to baseline (3.1±1.9 vs 4.3±2.3; P=0.02), while there was no change with amantadine (3.2±2.0 vs 3.6±2.2; P=0.58). Similar results were obtained in the per protocol population (3.1±1.9 vs 4.4±2.3; P=0.02 and 3.2±2.0 vs 3.6±2.2; P=0.58). Among the intent to treat population, there was no difference between the two treatment groups (P=0.14). Secondary: There was no significant difference of "on" time with troublesome dyskinesia from baseline to week three with placebo (1.7±1.8 vs 3.5±3.1 hours; P=0.01). Dyskinesia duration increased significantly with placebo (1.8±1.2 vs 2.5±1.2 hours; P=0.026). There were no changes between baseline and end of treatment in any other secondary outcome with either treatment. There were a total of six adverse events reported by patients during the three weeks. One patient receiving amantadine reported falls and one patient receiving placebo reported a worsening of painful "off" period dystonia during the night. Three patients discontinued treatment earlier due to a worsening of dyskinesias; two receiving placebo and one receiving amantadine.
Crosby et al[77] Amantadine as treatment for dyskinesia of idiopathic Parkinson's	MA Patients of all ages with a diagnosis of idiopathic Parkinson's	N=53 Durations of >4 weeks	Primary: Changes in dyskinesia rating scales, number of withdrawals due to	Primary: Two of the three trials could not be analyzed for efficacy because of a lack of a washout period prior to the XO. In regards to the first trial, two (8%) of the patients withdrew prior to the XO. In regards to the second one, four (22%) of the patients withdrew prior to the XO. Two of the patients complained of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
disease vs placebo	disease who had developed dyskinesia, patients were allowed to be on levodopa		lack of efficacy and/or adverse events Secondary: Not reported	confusion or hallucinations, one complained of nausea, and one complained of a recurrence of pre-existing palpitations. The third study included a one week XO period so it was eligible to be analyzed for efficacy. No difference was found between amantadine in the first or second treatment period. Amantadine was associated with a decrease in dyskinesia severity score by 6.4 points (41.0%) following the levodopa challenge compared to the placebo arm. One patient experienced reversible edema of both feet during active amantadine treatment. Secondary: Not reported
Paci et al[78] Amantadine as adjunctive therapy to current levodopa, carbidopa and dopamine agonist therapy for severe Parkinson's disease	OL Patients with advanced Parkinson's disease complicated by motor fluctuations and levodopa-induced dyskinesia	N=20 8 months	Primary: Unified Parkinson's disease rating scale, Dyskinesias Rating Scale and investigator global assessment scale Secondary: Not reported	Primary: Amantadine treatment was associated with a 38% reduction in motor fluctuations (P<0.001) and in the total dyskinesia score compared to baseline. Unified Parkinson's disease rating subscale IV mean scores decreased from 10 to six (P<0.001), and Dyskinesias Rating Scale mean scores decreased from 18.5 to 7.5 (P<0.001). The investigator global assessment scale for dyskinesia in patients using amantadine was rated 2.1. After two to eight months of treatment, dyskinesia scores increased to -2.2 leading to drug discontinuation in all patients. Secondary: Not reported
Pappa et al[79] Amantadine 100 to 400 mg/day for 2 weeks vs placebo for 2 weeks A 4-day washout period	DB, PC, XO Adult patients with schizophrenia, carried a diagnosis of tardive dyskinesia and had a stable psychiatric condition	N=22 4 weeks	Primary: Change from baseline Abnormal Involuntary Movement Scale score Secondary: Neuro-psychiatric functioning	Primary: With amantadine, patients exhibited a reduced average score of total (from 13.5 before treatment to 10.5 after treatment; P=0.000), facial and oral (5.5 to 4.2; P=0.002), extremity (4.18 to 2.80; P=0.000) and severity (2.04 to 1.54; P=0.002) Abnormal Involuntary Movement Scale scores. For the 22 patients, the average total score at baseline was 15.63 and after treatment with amantadine, the average total reduction was 21.81%. With placebo, no reduction was noted. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
was included between treatments.			assessed by the Brief Psychiatric Rating Scale, cognitive function assessed by the Mini-Mental State Examination; Clinical Global Impression; incapacitation; distress and Brief Psychiatric Rating Scale; safety	Amantadine exhibited a positive effect that was significant for incapacitation (P=0.008) and Clinical Global Impression. (P=0.000). It is noted within the trial that treatment did not alter distress (P=0.511), Brief Psychiatric Rating Scale (P=0.01) and Mini-Mental State Examination (P=0.001) scores. There were no serious adverse events with amantadine; however, the following minor adverse events were reported: insomnia (n=3), constipation (n=2) and dizziness (n=2). Headache (n=3) and dizziness (n=2) were reported with placebo.

*Not commercially available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, ITT=intention-to-treat, ITTI=intention-to-treat infected, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, RETRO=retrospective, SMD=standardized mean difference, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: ICU=intensive care unit, NI=neuraminidase inhibitors, PEP=post-exposure prophylaxis

Special Populations

Table 6. Special Populations[3,4,8,9,10,12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Amantadine	Dose should be reduced in patients ≥65 years of age. Safety and efficacy in children <1 year of age have not been established.	For creatinine clearances 30 to 50 mL/minute, 200 mg on day one then 100 mg daily is recommended; for creatinine clearances 15 to 29 mL/minute, 200 mg on day one then 100 mg on alternate days is recommended; for creatinine clearances <15 mL/minute, 200 mg every seven days is recommended.	No dosage adjustment is required; care should be exercised.	C	Yes; use is not recom-mended in nursing mothers.
Oseltamivir	No dosage adjustment required in the elderly population. Safety and efficacy in elderly residents of nursing homes for the prophylaxis of influenza have been established. Safety and efficacy in children <2 weeks of age have not been established.	For creatinine clearances 10 to 30 mL/minute, 75 mg once daily for five days is recommended for treatment and 75 mg every other day or 30 mg once daily is recommended for prophylaxis.	No dosage adjustment is required in patients with mild to moderate hepatic impairment.	C	Unknown
Rimantadine	For geriatric (elderly nursing home) patients 100 mg once daily is recommended. Safety and efficacy in children for the treatment of influenza A infection have not been established. Safety and efficacy in	For creatinine clearances ≤10 mL/minute 100 mg once daily is recommended.	A dose reduction to 100 mg once daily is recom-mended for severe hepatic dysfunction.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	children <1 year of age for the prophylaxis of influenza have not been established.				
Zanamivir	No dose adjustment required in the elderly population. Efficacy in nursing home patients for the prophylaxis of influenza has not been established. Safety and efficacy in children <7 years of age for the treatment of influenza and in children <5 years of age for the prophylaxis of influenza have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown

Adverse Drug Events

Table 7. Adverse Drug Events (%)[3,4,8,9,10,12]

Adverse Effect	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Cardiovascular				
Arrhythmia	✔	✔	-	✔
Cardiac failure/arrest	✔	-	<0.3	-
Congestive heart failure	0.1 to 1.0	-	-	-
Edema	✔	-	-	-
Heart block	-	-	<0.3	-
Hypertension	0.1 to 1.0	-	-	-
Orthostatic hypotension	1 to 5	-	-	-
Palpitation	-	-	<0.3	-
Pedal edema	-	-	<0.3	-
Peripheral edema	1 to 5	-	-	-
Unstable angina	-	≤1	-	-
Central Nervous System				
Aggressive behavior	✔	-	-	-
Agitation	1 to 5	✔	0.3 to 1.0	✔
Amnesia	0.1 to 1.0	-	-	-
Anxiety	1 to 5	✔	-	✔
Ataxia	1 to 5	-	0.3 to 1.0	-
Coma	✔	-	-	-
Confusion	1 to 5	-	<0.3	-
Convulsion	<0.1	-	<0.3	-
Delirium	✔	✔	-	✔
Delusions	✔	-	-	-

Adverse Effect	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Depression	1 to 5	-	0.3 to 1.0	-
Dizziness	5 to 10	1 to 2	0.7 to 1.9	<1
Dream abnormality	1 to 5	-	-	-
Euphoria	0.1 to 1.0	-	<0.3	-
Gait abnormality	✔	-	<0.3	-
Hallucinations	1 to 5	✔	<0.3	✔
Headache	1 to 5	2 to 18	1.4	2 to 24
Hyperkinesia	0.1 to 1.0	-	<0.3	-
Hypertonia	✔	-	-	-
Hypokinesia	✔	-	-	-
Manic reaction	✔	-	-	-
Nervousness	1 to 5	-	1.3 to 2.1	-
Nightmares	-	-	-	✔
Paranoid reaction	✔	-	-	-
Psychosis	0.1 to 1.0	-	-	-
Pyrexia	-	≤1 to 9	-	<1.5 to 4.0
Seizure	-	✔	-	✔
Somnolence	1 to 5	-	0.3 to 1.0	-
Stupor	✔	-	-	-
Thinking abnormality	0.1 to 1.0	-	-	-
Tremor	✔	-	<0.3	-
Vertigo	-	1	-	-
Dermatological				
Anaphylactoid reactions	✔	✔	-	✔
Dermatitis	-	1	-	-
Eczema	-	✔	-	✔
Eczematoid dermatitis	<0.1	-	-	-
Erythema multiforme	-	✔	-	✔
Livedo reticularis	1 to 5	-	-	-
Pruritus	✔	-	-	-
Rash	0.1 to 1.0	✔	-	✔
Steven-Johnson Syndrome	-	✔	-	✔
Toxic epidermal necrolysis	-	✔	-	✔
Urticaria	-	✔	-	<1.5
Gastrointestinal				
Abdominal pain	-	2 to 5	1.4	<1.5
Anorexia	1 to 5	-	1.6	-
Constipation	1 to 5	-	-	-
Diarrhea	1 to 5	3 to10	0.3 to1.0	2 to 4
Dyspepsia	-	-	0.3 to1.0	-
Dysphagia	✔	-	-	-
Gastrointestinal bleeding	-	✔	-	-
Nausea	5 to 10	3 to 10	2.8	2 to 3
Pseudomembranous colitis	-	≤1	-	-
Vomiting	0.1 to 1.0	2 to 15	1.7	2
Respiratory				
Acute respiratory failure	✔	-	-	-
Asthma	-	1 to 3	-	2
Bronchitis	-	1 to 2	-	3
Bronchospasm	-	-	<0.3	✔
Cough	-	1 to 5	<0.3	3 to 17

Adverse Effect	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Dry mouth	1 to 5	-	1.5	-
Dry nose	1 to 5	-	-	-
Dyspnea	0.1 to 1.0	-	0.3 to1.0	✔
Ear, nose & throat infections	-	-	-	2 to 5
Nasal signs and symptoms	-	-	-	3 to12
Pneumonia	-	≤1 to 2	-	-
Pulmonary edema	✔	-	-	-
Sinusitis	-	2	-	2
Tachypnea	✔	-	-	-
Throat and tonsil discomfort and pain	-	-	-	8 to 19
Viral respiratory infections	-	-	-	3 to 13
Miscellaneous				
Abnormal liver function tests	✔	✔	-	✔
Aggravation of diabetes	-	✔	-	-
Agranulocytosis	✔	-	-	-
Allergic reactions	✔	-	-	-
Anemia	-	≤1	-	-
Arthralgia/myalgia	-	-	-	<1.5 to 8.0
Asthenia	-	-	1.4	-
Cerebrovascular disorder	-	-	<0.3	-
Conjunctivitis	-	1	-	-
Ear disorder	-	2	-	-
Electroencephalography changes	✔	-	-	-
Epistaxis	-	1 to 3	-	-
Fatigue	1 to 5	1 to 8	1	<1.5 to 8.0
Fever	✔	-	-	-
Hepatitis	-	✔	-	-
Humerus fracture	-	≤1	-	-
Insomnia	5 to 10	1	2.1 to 3.4	-
Involuntary muscle contractions	✔	-	-	-
Keratitis	✔	-	-	-
Leukocytosis	✔	-	-	-
Leukopenia	<0.1	-	-	-
Libido decreased	0.1 to 1.0	-	-	-
Libido increased	✔	-	-	-
Lymphadenopathy	-	✔	-	-
Mydriasis	✔	-	-	-
Neutropenia	<0.1	-	-	✔
Non-puerperal lactation	-	-	<0.3	-
Oculogyric episodes	<0.1	-	-	-
Otitis media	-	2 to 9	-	-
Pallor	-	-	<0.3	-
Paresthesia	✔	-	-	-
Parosmia	-	-	<0.3	-
Pathological gambling	✔	-	-	-
Peritonsillar abscess	-	≤1	-	-
Slurred speech	0.1 to 1.0	-	-	-
Suicide/suicidal attempt/suicidal ideation	<0.1	-	-	-
Taste loss/change	-	-	<0.3	-
Tympanic membrane disorder	-	1	-	-
Urinary retention	0.1 to 1.0	-	-	-

Adverse Effect	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Visual disturbance	0.1 to 1.0	-	-	-
Weakness	0.1 to 1.0	-	-	-

✔ Percent not specified.
- Event not reported.

Contraindications

Table 8. Contraindications[3,4,8,9,10,12]

Contraindication	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Hypersensitivity to drugs of the amantadine class	-	-	✔	-
Hypersensitivity to milk proteins	-	-	-	✔
Known hypersensitivity to any ingredients contained in the product	✔	✔	✔	✔

Warnings/Precautions

Table 9. Warnings and Precautions[3,4,8,9,10,12]

Warnings/Precautions	Amantadine	Oseltamivir	Rimantadine	Zanamivir
Abrupt discontinuation; patients have experienced a parkinsonian crisis (e.g., a sudden marked clinical deterioration)	✔	-	-	-
Allergic reactions; oropharyngeal edema, serious skin rashes and anaphylaxis have been reported in postmarketing experience	-	-	-	✔
Bacterial infections; infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza	-	✔	-	✔
Bronchospasm; serious cases of bronchospasm, including fatalities, have been reported during treatment of patients with and without underlying airways disease	-	-	-	✔
Cardiac disease; efficacy of influenza treatment in this population has not been established	-	✔	-	-
Central nervous system events; patients should be cautioned against driving or working in situations where alertness and adequate motor coordination are important	✔	-	-	-
Congestive heart failure or peripheral edema; patients should be closely monitored while receiving treatment	✔	-	-	-
Death has been reported with overdose	✔	-	-	-
Epilepsy; patients with a history of epilepsy or other seizures should be observed closely for possible increased seizure activity	✔	-	✔	-
Hepatic impairment; rare instances of reversible elevation of liver enzymes have	✔	-	-	-

Warnings/Precautions	Amantadine	Oseltamivir	Rimantadine	Zanamivir
been reported				
Immunocompromised patients; efficacy of influenza treatment or prophylaxis in this population has not been established	-	✔	-	-
Melanoma; patients with Parkinson's disease have a higher risk of developing melanoma than the general population	✔	-	-	-
Neuroleptic malignant syndrome; cases have been reported following dose reduction or withdrawal of amantadine therapy	✔	-	-	-
Neuropsychiatric events; neurologic and behavioral symptoms including hallucinations, delirium, and abnormal behavior have been reported, and in some cases result in fatal outcomes	-	✔	-	✔
Renal impairment; reduce dosage in patients with renal impairment	✔	-	-	-
Respiratory disease; efficacy of influenza treatment in this population has not been established	-	✔	-	-
Serious skin/hypersensitivity reactions; cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience	-	✔	-	-
Suicide attempts and suicidal ideation have been reported in patients with and without prior history of psychiatric illness	✔	-	-	-
Untreated closure angle glaucoma; anticholinergic effects of treatment may cause mydriasis	✔	-	-	-

Drug Interactions

Table 10. Drug Interactions[3,4,8,9,10,12]

Generic Name	Interacting Medication or Disease	Potential Result
Antivirals (all)	Influenza virus vaccine, live	The clinical effect of live attenuated influenza virus vaccine may be decreased by antivirals.
Amantadine	Anticholinergic agents	Concurrent administration may potentiate the anticholinergic-like adverse events of amantadine. Consider reducing the dose of the anticholinergic agent if atropine-like events appear.
Amantadine	Central nervous system stimulants	Careful observation is required during concomitant administration.
Amantadine	Quinidine, quinine	Coadministration was shown to reduce renal clearance of amantadine.
Amantadine	Sulfamethoxazole/ trimethoprim	Coadministration may impair renal clearance of amantadine, resulting in higher plasma concentrations.
Amantadine	Thioridazine	Coadministration of thioridazine has been reported to worsen the tremor in elderly patients with Parkinson's

Generic Name	Interacting Medication or Disease	Potential Result
		disease; however, it is not known if other phenothiazines produce a similar response.
Amantadine	Triamterene, thiazide diuretics	Coadministration resulted in a higher plasma amantadine concentration.

Dosage and Administration

Table 11. Dosing and Administration[3,4,8,9,10,12]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Amantadine	Prophylaxis against signs and symptoms of influenza A virus infection, treatment of uncomplicated respiratory tract illness caused by influenza A virus: Capsule, oral syrup, tablet: 200 mg QD or 100 mg BID Treatment of parkinsonism (monotherapy): Capsule, oral syrup, tablet: 100 mg BID; may titrate up to 400 mg/day in divided doses Treatment of parkinsonism (concomitant therapy): Capsule, oral syrup, tablet: 100 mg QD; may titrate to 100 mg BID Treatment of drug-induced extrapyramidal reactions: Capsule, oral syrup, tablet: 100 mg BID; maximum 300 mg/day in divided doses	Prophylaxis against signs and symptoms of influenza A virus infection, treatment of uncomplicated respiratory tract illness caused by influenza A virus in children one to nine years of age: Capsule, oral syrup, tablet: 4.4 to 8.8 mg/kg/day divided BID (not to exceed 150 mg/day), Prophylaxis against signs and symptoms of influenza A virus infection, treatment of uncomplicated respiratory tract illness caused by influenza A virus in children nine to 12 years of age: Capsule, oral syrup, tablet: 100 mg BID	Capsule: 100 mg Oral syrup: 50 mg/5 mL Tablet: 100 mg
Oseltamivir	Prophylaxis of influenza: Capsule, powder for oral suspension: 75 mg QD for at least 10 days (up to six weeks); therapy should begin within two days of exposure; the duration of prophylaxis is at least 10 days following a close contact and up to six weeks during a community outbreak; safety has been demonstrated for up to 12 weeks in immunocompromised patients Treatment of acute, uncomplicated illness due to influenza infection in patients who have been symptomatic for	Prophylaxis of influenza in children one year of age and older: Capsule, powder for oral suspension: ≤15 kg, 30 mg QD for 10 days; 15.1 to 23 kg, 45 mg QD for 10 days; 23.1 to 40 kg, 60 mg QD for 10 days; ≥40.1 kg, 75 mg QD for 10 days; begin prophylaxis within two days of a close-contact exposure and continue for 10 days; for prophylaxis in pediatric patients during a community outbreak of influenza, dosing may be continued for up to six weeks	Capsule: 30 mg 45 mg 75 mg Powder for oral suspension: 6 mg/mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	no more than two days: Capsule, powder for oral suspension: 75 mg BID for five days	Treatment of acute, uncomplicated illness due to influenza infection in patients two weeks of age and older who have been symptomatic for no more than two days: Capsule, powder for oral suspension: less than one year, 3 mg/kg BID for five days; one to twelve years, ≤15 kg, 30 mg BID for five days; 16 to 23 kg, 45 mg BID for five days; 24 to 40 kg, 60 mg BID for five days; ≥41 kg, 75 mg BID for five days; treatment should begin within two days of developing symptoms	
Rimantadine	Prophylaxis against signs and symptoms of influenza A virus infection: Tablet: 100 mg BID Treatment of illness caused by various strains of influenza A virus in adults: Tablet: 100 mg BID; therapy should be initiated as soon as possible, preferably within 48 hours after onset of signs and symptoms of influenza A; therapy should be continued for approximately seven days from the initial onset of symptoms	Prophylaxis against signs and symptoms of influenza A virus infection in children one year of age and older: Tablet: less than 10 years, 5 mg/kg QD; maximum, 150 mg/day; 10 years of age and older, 100 mg BID Safety and efficacy in children for the treatment of influenza A infection have not been established.	Tablet: 100 mg
Zanamivir	Prophylaxis of influenza‡: Blister for oral inhalation: two inhalations (5 mg/inhalation) QD for 10 days (household setting) or for 28 days (community setting) Treatment of uncomplicated acute illness due to influenza A and B in adults who have been symptomatic for no more than two days: Blister for oral inhalation: two inhalations (5 mg/inhalation) every 12 hours for five days; initiate within two days of symptom onset and when possible, administer two doses on day one, at least two hours apart; subsequently, doses	Prophylaxis of influenza in children five years of age and older‡: Blister for oral inhalation: household setting, two inhalations (5 mg/inhalation) QD for 10 days Treatment of uncomplicated acute illness due to influenza A and B in children seven years of age and older who have been symptomatic for no more than two days: Blister for oral inhalation: two inhalations (5 mg/inhalation) every 12 hours for five days; initiate within two days of symptom onset and when possible, administer two doses on day one, at least two hours apart;	Blister for oral inhalation: 5 mg/ actuation

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	should be administered 12 hours apart; data is lacking on the effectiveness if treatment is initiated more than two days after the onset of signs or symptoms	subsequently, doses should be administered 12 hours apart; data is lacking on the effectiveness if treatment is initiated more than two days after the onset of signs or symptom	

BID=twice daily, QD=once daily
†There is no data on the effectiveness of prophylaxis in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case. There is no data on the effectiveness of prophylaxis in a community outbreak when initiated more than five days after the outbreak was identified in the community.
‡ The dose should be given at approximately the same time each day and should be administered under adult supervision and instruction. Data is lacking on the effectiveness of prophylaxis if initiated more than 36 hours after the onset of signs or symptoms.

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: **Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014–15 Influenza Season (2014)**[80]	• For 2014–15, U.S.-licensed influenza vaccines will contain the same vaccine virus strains as those in the 2013–14 vaccine. Trivalent influenza vaccines will contain hemagglutinin (HA) derived from an A/California/7/2009 (H1N1)-like virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like (Yamagata lineage) virus. Quadrivalent influenza vaccines will contain these antigens, and also a B/Brisbane/60/2008-like (Victoria lineage) virus. Recommendations for vaccination • Routine annual influenza vaccination is recommended for all persons six months of age and older. • Vaccination should optimally occur before onset of influenza activity in the community, and providers should offer vaccination as soon as vaccine is available. • Vaccination also should continue to be offered throughout the influenza season. • Children aged six months through eight years who require two doses should receive their first dose as soon as possible after vaccine becomes available, and the second dose ≥4 weeks later. Vaccine doses for children aged six months through eight years • Children aged six months through eight years require two doses of influenza vaccine (administered a minimum of four weeks apart) during their first season of vaccination. • In determining the appropriate number of doses, previous receipt of vaccine containing 2009 influenza A(H1N1) pandemic antigen (included in monovalent pandemic vaccine during 2009–10 and in seasonal influenza vaccines since the 2010–11 season) also should be considered. In addition, because the strains contained in the 2014–15 seasonal influenza vaccines are identical to those contained in the 2013–14 vaccines, only 1 dose is required for any child aged six months through eight years who previously received ≥1 dose of 2013–14 seasonal influenza vaccine. Live attenuated vaccine versus inactivated vaccine considerations • Both live and attenuated have demonstrated effectiveness in children and adults; however, several studies showed that live vaccines were

Clinical Guideline	Recommendation(s)
	more effective in children. • Live attenuated vaccines should be given to: o Persons aged <2 years or >49 years o Those with contraindications listed in the package insert (children aged 2 to 17 years who are receiving aspirin or aspirin-containing products; persons who have experienced severe allergic reactions to the vaccine or any of its components, or to a previous dose of any influenza vaccine) o Pregnant women o Immunosuppressed persons o Persons with a history of egg allergy o Children aged two through four years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months. (For those aged ≥5 years with asthma, recommendations are described below) o Persons who have taken influenza antiviral medications within the previous 48 hours. • Persons of any age with asthma might be at increased risk for wheezing after administration of live virus • Persons who care for severely immunosuppressed persons who require a protective environment should not receive live virus, or should avoid contact with such persons for seven days after receipt, given the theoretical risk for transmission of the live attenuated vaccine virus. <u>Influenza vaccination of persons with a history of egg allergy</u> • With the exceptions of trivalent recombinant influenza vaccine (RIV3) and cell culture-based inactivated influenza vaccine (ccIIV3), currently available influenza vaccines are prepared by propagation of virus in embryonated chicken eggs. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Because relatively few data are available for use of live attenuated influenza vaccine in this setting, IIV or RIV3 should be used. RIV3 may be used for persons aged 18 through 49 years who have no other contraindications. However, IIV (egg- or cell-culture based) may also be used, with the following additional safety measures: o Vaccine should be administered by a health care provider familiar with the potential manifestations of egg allergy. o Vaccine recipients should be observed for ≥30 minutes for signs of a reaction after administration of each vaccine dose. • Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may receive RIV3 if they are aged 18 through 49 years and there are no other contraindications. If RIV3 is not available or the recipient is not within the indicated age range, IIV should be administered by a physician with experience in the recognition and management of severe allergic conditions. • Regardless of allergy history, all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available.

Clinical Guideline	Recommendation(s)
	• Persons who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be allergic. Egg-allergic persons might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy. Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus skin and/or blood testing for immunoglobulin E directed against egg proteins. • For persons with no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained before vaccination. Alternatively, RIV3 may be administered if the recipient is aged 18 through 49 years. • A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine. Quadrivalent influenza vaccines • All currently available influenza vaccines are trivalent and contain A(H1N1), A(H3N2), and B viral antigens. There are two antigenically distinct lineages of influenza B viruses referred to as Victoria and Yamagata lineages. • Immunization against B virus strains of one lineage provides limited cross-protection against strains in the other lineage. Because of this and the difficulty of predicting which B virus lineage will predominate during a given season, inclusion of a second influenza B vaccine virus strain in seasonal influenza vaccines has been proposed. • In February 2012, FDA approved a new seasonal quadrivalent LAIV, FluMist Quadrivalent®. • This vaccine currently is not anticipated to be available until the 2013-2014 influenza season, at which time it is expected to replace the currently available seasonal trivalent FluMist® formulation. • Inactivated quadrivalent influenza vaccines currently are in development.
Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: Prevention and Control of Seasonal Influenza with Vaccines: **Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014 (2013)**[81]	Influenza Vaccines and Use of Influenza Antiviral Medications • Administration of IIV to persons receiving influenza antiviral drugs for treatment or chemoprophylaxis is acceptable. • The effect on safety and effectiveness of live virus co-administration with influenza antiviral medications has not been studied. • Because antiviral drugs reduce replication of influenza viruses, live virus should not be administered until 48 hours after cessation of influenza antiviral therapy. • If influenza antiviral medications are administered within two weeks after receipt of live virus, the live virus dose should be repeated 48 or more hours after the last dose of antiviral medication. • Persons receiving antiviral drugs within the period two days before to 14 days after vaccination with live virus may be revaccinated another approved vaccine formulation (e.g., IIV or RIV).
American Academy of Pediatrics: **Recommendations for**	• The American Academy of Pediatrics recommends immunization for all children and adolescents six months of age and older during the 2013-2014 influenza season.

Clinical Guideline	Recommendation(s)
Prevention and Control of Influenza in Children, 2013-2014 (2013)[82]	• Special effort should be made to vaccinate the following groups: o All children, including infants born preterm, who are six months of age and older with conditions that increase the risk of complications from influenza (eg, children with chronic medical conditions, such as asthma, diabetes mellitus, hemodynamically significant cardiac disease, immunosuppression, or neurologic and neurodevelopmental disorders), o Children of American Indian/Alaskan Native heritage, o All household contacts and out-of-home care providers of children with high-risk conditions and children younger than five years, especially infants younger than six months, o All health care personnel (HCP), o All women who are pregnant, are considering pregnancy, have recently delivered, or are breastfeeding during the influenza season. • The number of seasonal influenza vaccine doses to be administered in the 2013–2014 influenza season depends on the child's age at the time of the first administered dose and his or her vaccine history: o Influenza vaccines are not licensed for administration to infants younger than 6 months of age. o Children 9 years and older need only 1 dose. o Children 6 months through 8 years of age receiving the seasonal influenza vaccine for the first time should receive a second dose this season at least 4 weeks after the first dose. o Children 6 months through 8 years of age who received seasonal influenza vaccine before the 2013–2014 influenza season: ▪ Need only 1 dose of vaccine, if they previously received 2 or more doses of seasonal vaccine since July 1, 2010. ▪ Need 2 doses of vaccine, if they have not previously received 2 or more doses of seasonal vaccine since July 1, 2010. ▪ need only 1 dose of influenza vaccine if there is clear documentation of having received at least 2 seasonal influenza vaccines from any previous season and at least 1 dose of a pH1N1-containing vaccine, which could have been in 1 of the seasonal vaccines (2010–2011, 2011–2012, or 2012–2013) or as the monovalent pH1N1 vaccine from 2009–2010. • Vaccination should not be delayed to obtain a specific product for either dose. Any available, age-appropriate trivalent or quadrivalent vaccine can be used. A child who receives only 1 of the 2 doses as a quadrivalent formulation is likely to be less primed against the additional B virus. • As soon as the seasonal influenza vaccine is available locally, HCP should be immunized, parents and caregivers should be notified about vaccine availability, and immunization of all children 6 months and older, especially children at high risk of complications from influenza, should begin. • Providers should continue to offer vaccine until the vaccine expiration date because influenza is unpredictable. Protective immune responses

Clinical Guideline	Recommendation(s)
	persist throughout the influenza season, which can have >1 disease peak and often extends into March or later. Use of antiviral medications • Antiviral medications also are important in the control of influenza but are not a substitute for influenza immunization. • The neuraminidase inhibitors oseltamivir and zanamivir are the only antiviral medications routinely recommended for chemoprophylaxis or treatment during the 2013-2014 season. • Recent viral surveillance and resistance data indicate that the majority of currently circulating influenza viruses likely to cause 2013–2014 seasonal influenza in North America continue to be sensitive to oseltamivir and zanamivir. • Amantadine and rimantadine should not be used because circulating influenza A viruses have sustained high levels of resistance to these drugs, and they are not effective against influenza B viruses. • immunization. • Influenza vaccine should always be offered when not contraindicated, even when influenza virus is circulating in the community. • Antiviral medications currently licensed are important adjuncts to influenza immunization for control and prevention of influenza disease, but there are toxicities associated with antiviral agents and indiscriminate use might limit availability.
Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: **Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (2011)**[15]	• Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. • Antiviral treatment is recommended as soon as possible for: o Patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization. o Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions. • Persons at higher risk for influenza complications recommended for antiviral treatment include: o Children less than two years of age. o Adults aged ≥65 years. o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury). o Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus (HIV) infection. o Women who are pregnant or postpartum (within two weeks after delivery). o Persons aged <19 years who are receiving long-term aspirin therapy. o American Indians/Alaska Natives.

Clinical Guideline	Recommendation(s)
	o Persons who are morbidly obese (i.e., body-mass index ≥40). o Residents of nursing homes and other chronic-care facilities. • Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Oseltamivir and zanamivir, neuraminidase inhibitors are active against both influenza A and B. Rimantadine and amantadine are only active against influenza A. • Recommended antiviral medications include oseltamivir and zanamivir. Greater than 99% of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs. Local antiviral resistance surveillance data should be monitored. Currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes. These medications are not recommended for use against influenza A virus infections. • Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants less than one year of age when indicated. • Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status. The greatest benefit is when initiated within 48 hours of influenza onset. However, it may be beneficial in those with severe, complicated, or progressive illness and in hospitalized patients if administered >48 hours from onset. Health-care providers and patients should make this decision on an individual basis. • Randomized, controlled trials conducted primarily among persons with mild illness in outpatient settings have demonstrated that zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day when administered within 48 hours of illness onset compared to placebo. • Data are limited about the effectiveness of zanamivir and oseltamivir treatment in preventing serious influenza-related complications. • Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. • Post-exposure chemoprophylaxis lowers but does not eliminate the risk for influenza. Susceptibility to influenza returns once the antiviral medication is stopped, and influenza vaccination is recommended. Duration should be for a total of no more than 10 days after the most recent known exposure to a close contact known to have influenza. • Pre-exposure chemoprophylaxis must be administered for the duration of time when exposure might occur and should only be used for persons who are at very high risk for influenza-related complications who cannot otherwise be protected during times when a high risk for exposure exists. The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. • Zanamivir is approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. It is also approved for treatment of influenza among children seven years of age and older and for chemoprophylaxis of influenza among children five years of age and older. • Oseltamivir is approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for

Clinical Guideline	Recommendation(s)
	chemoprophylaxis of influenza among adults. It is also approved for the treatment and chemoprophylaxis of influenza among children one year of age and older. • Rimantadine is Food and Drug Administration (FDA) approved for children one year of age and older and for treatment and chemoprophylaxis of only influenza A virus infections among adults. Use of rimantadine among children less than one year of age has not been evaluated adequately. • Oseltamivir, zanamivir, and rimantadine are "Pregnancy Category C" medications. Oseltamivir is preferred for treatment of pregnant women. 2009 Influenza A (H1N1) • In the post-pandemic period, 2009 H1N1 virus strains now are considered to be the predominant seasonal influenza A (H1N1) virus strains. • Reverse transcription polymerase chain reaction is the most accurate and sensitive test for detecting influenza viruses, including the 2009 H1N1 virus. • Epidemiologic studies of seasonal influenza or 2009 H1N1 suggest that persons at higher risk for influenza complications include: o Children less than five years of age (especially those less than two years of age). o Adults aged ≥65 years. o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury). o Persons with immunosuppression, including that caused by medications or by HIV infection. o Women who are pregnant or postpartum (within two weeks after delivery). o Persons aged ≤18 years who are receiving long-term aspirin therapy. o American Indians/Alaska Natives. o Persons who are morbidly obese (i.e., body mass index ≥40). o Residents of nursing homes and other chronic-care facilities. • Studies conducted during the 2009 influenza A (H1N1) pandemic indicate that viral shedding, clinical illness, and transmissibility in a household setting are similar compared to seasonal influenza. • During the 2009 H1N1 pandemic, the clinical syndrome most likely to be the cause of hospitalization was diffuse viral pneumonitis, which in some instances led to shock and respiratory failure. • Influenza complications among children during the 2009 influenza A (H1N1) pandemic were generally similar to those observed among children with seasonal influenza. However, much higher rates of illness among children observed during the 2009 H1N1 pandemic compared to most influenza seasons resulted in much higher rates of children hospitalized with complications.

Clinical Guideline	Recommendation(s)
	• Circulating 2009 H1N1 virus strains are resistant to adamantanes. These are not recommended for treatment or prophylaxis. • The World Health Organization (WHO) has recommended empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection that are at increased risk for influenza complications. • Similar recommendations were made by Centers for Disease Control and Prevention (CDC) during the 2009 H1N1 pandemic and the subsequent 2009-2010 influenza season. • Oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1. • Those with a potential exposure to a person with laboratory-confirmed 2009 H1N1 should receive chemoprophylaxis. • Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified. • Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare but has been documented. • Nearly all sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections identified to date also have been associated with the H275Y mutation in neuraminidase; these oseltamivir-resistant H275Y virus infections are susceptible to zanamivir. • Intravenous zanamivir is the recommended antiviral treatment for severely ill patients with highly suspected or confirmed oseltamivir-resistant 2009 H1N1 virus infection. • As of December 2010, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide. • During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children less than one year of age were developed, on the basis of very limited pharmacokinetic data. • The Emergency Use Authorization issued during the 2009 H1N1 pandemic for this indication expired on June 23, 2010, but recommendations on dosing for children less than one year of age are available. • CDC recommends that clinicians who treat children aged three to 11 months administer 3 mg/kg/dose twice per day for treatment, and 3 mg/kg/dose once per day for chemoprophylaxis. • Infants less than three months of age are recommended to receive 3 mg/kg/dose twice per day for treatment. However, chemoprophylaxis for infants less than three months of age is not recommended unless the exposure situation was judged to be critical, because of a lack of data on use of oseltamivir on this age group. • WHO subsequently recommended that children aged <14 days who are being treated for suspected or confirmed influenza receive 3 mg/kg/dose once daily. Lower doses should be considered for infants who are not receiving regular oral feedings or those who have substantially reduced renal function.
Infectious Diseases Society of America: **Seasonal Influenza in Adults and Children-Diagnosis, Treatment, Chemoprophylaxis,**	<u>Antivirals for treatment</u> • Treatment is recommended for adults and children with influenza virus infection who meet the following criteria: o Patients with laboratory-confirmed or highly susceptible influenza virus infection at high risk for developing complications within 48 hours after symptom onset. Treatment

Clinical Guideline	Recommendation(s)
and Institutional Outbreak Management: Clinical Practices Guidelines of the Infectious Diseases Society of America (2009)[83]	is recommended regardless of influenza vaccination status and severity of illness. o Patients requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 hours after onset of symptoms. • Treatment should be considered for adults and children with influenza virus infection who meet the following criteria: o Outpatients at high risk of complications, with illness that is not improving and with a positive influenza test result from a specimen obtained >48 hours after symptom onset. o Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk for complications, whose symptom onset is <48 hours before presentation and who wish to shorten the duration of illness and to further reduce their relatively low risk of complications or who are in close contact with persons at high risk of complications secondary to influenza infection. • Patients at high risk for complications from influenza include: o Unvaccinated infants 12 to 24 months old. o Patients with asthma or other chronic pulmonary diseases. o Patients with hemodynamically significant cardiac disease. o Patients who have immunosuppressive disorders or who are receiving immunosuppressive therapy. o HIV infected patients. o Patients with sickle cell anemia and other hemoglobinopathies. o Patients with diseases requiring long term aspirin therapy. o Patients with chronic renal dysfunction. o Patients with cancer. o Patients with chronic metabolic disease. o Patients with neuromuscular disorders, seizure disorders or cognitive dysfunction that may compromise the handling of respiratory secretions. o Patients ≥65 years old. o Residents of any age in nursing homes or other long term care institutions. • On the basis of antiviral susceptibility patterns current as of March 2009: o Influenza A (H1N1) virus infections should be treated with either zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile). Oseltamivir should not be used. o Influenza A (H3N2) virus infections should be treated with oseltamivir or zanamivir. The adamantanes should not be used. o If subtype information is unavailable, influenza A should be treated with either zanamivir or combination oseltamivir and rimantadine therapy. o Influenza B virus infection should be treated with oseltamivir or zanamivir. <u>Antivirals for chemoprophylaxis</u> • Antiviral chemoprophylaxis is not a substitute for influenza vaccination, which is the primary tool to prevent influenza.

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	• When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high risk patients during the two weeks after vaccination before an adequate immune response to inactivated vaccine develops. • Antiviral chemoprophylaxis should be considered for adults and children at least one year old who are at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness. • Antiviral chemoprophylaxis, in conjunction with prompt administration of the inactivated vaccine, should be considered for adults and children at least one year old who are at high risk of developing complications from influenza virus infection and have not yet received influenza vaccine when influenza activity has already been detected in the community. • Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children at least one year old who are in close contact with patients at high risk of developing influenza complications during periods of influenza activity. • Antiviral chemoprophylaxis is recommended for all residents, vaccinated and unvaccinated, in institutions (i.e., nursing homes, long term care facilities) that are experiencing influenza outbreaks. • The strongest consideration for use of antiviral chemoprophylaxis should be given to patients at the highest risk of influenza-associated complications. • Antiviral chemoprophylaxis should be considered for patients at high risk of developing complications from influenza if influenza vaccine is not available due to a shortage. • Antiviral chemoprophylaxis can be considered for high risk patients in situations where there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains. • Antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity in patients at high risk of complications who are not adequately protected as a result of poor immune response, lack of influenza vaccination or ineffective vaccine. • Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when one family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants less than six months old. o In this setting, all non-infected family members should receive antiviral chemoprophylaxis. o All eligible family members in this settings should be vaccinated, making chemoprophylaxis unnecessary. • Antiviral chemoprophylaxis and other control measures should be initiated in institutions when an influenza outbreak is detected or when influenza is strongly suspected but the etiology of the outbreak is unknown. • If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped after two weeks for patients in non-institutional settings. At least six weeks of chemoprophylaxis will be required for children less than nine years of age. • When antiviral chemoprophylaxis is used in a household after the

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	diagnosis of influenza in one family member, chemoprophylaxis should be continued for 10 days. • In patients at high risk for complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness, chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season. • On the basis of antiviral susceptibility patterns current as of March 2009: o For influenza A (H1N1), zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile) should be used for chemoprophylaxis. Oseltamivir should not be used. o For influenza A (H3N2), oseltamivir or zanamivir should be used for chemoprophylaxis. The adamantanes should not be used. o If subtype information is unavailable, either zanamivir or combination oseltamivir and rimantadine therapy should be used for influenza A chemoprophylaxis. o Oseltamivir or zanamivir should be used for influenza B chemoprophylaxis. <u>Outbreak management in institutional settings</u> • All residents with laboratory-confirmed influenza virus infection should be treated with an appropriate influenza antiviral medication. • After one case of laboratory-confirmed influenza, all patients in the facility subsequently developing influenza-like illness should be considered for treatment. • During documented outbreaks of influenza in long term care facilities, all resident should receive influenza antiviral chemoprophylaxis, regardless of influenza vaccination status. • For all institutional employees who are unable to receive influenza vaccine or for whom vaccine is contraindicated or expected to be ineffective, antiviral chemoprophylaxis should be administered. • Antiviral chemoprophylaxis should be continued for 14 days or for seven days after the onset of symptoms in the last person infected, whichever is longer.
World Health Organization Rapid Advice Guideline Panel on Avian Influenza: **World Health Organization Rapid Advice Guidelines for Pharmacological Management of Sporadic Human Infection with Avian Influenza A (H5N1) Virus (2007)**[84]	• Clinicians should administer oseltamivir treatment as soon as possible in patients with confirmed or strongly suspected H5N1 infection (strong recommendation, very low quality evidence). • Clinicians might administer zanamivir in patients with confirmed or strongly suspected infection with H5N1 virus (weak recommendation, very low quality evidence). • Clinicians should not administer amantadine or rimantadine alone as first-line treatment to patients with confirmed or strongly suspected human infection with H5N1 if neuraminidase inhibitors are available (strong recommendation, very low quality evidence). • Clinicians might administer amantadine or rimantadine as a first-line treatment to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible (weak recommendation, very low quality evidence). • Clinicians might administer a combination of a neuraminidase inhibitor

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	and amantadine or rimantadine to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are available and especially if the virus is known or likely to be susceptible (weak recommendation, very low quality evidence). • Oseltamivir or zanamivir should be administered as chemoprophylaxis continuing for seven to 10 days after the last known exposure in high-risk exposure groups (strong recommendation, very low quality evidence). • Oseltamivir or zanamivir might be administered as chemoprophylaxis continuing for seven to 10 days after the last known exposure in moderate-risk exposure groups (weak recommendation, very low quality evidence). • Oseltamivir or zanamivir should probably not be administered as chemoprophylaxis in low-risk exposure groups (weak recommendation, very low quality evidence). • Amantadine or rimantadine should not be administered as chemoprophylaxis against human infection with H5N1 if the virus is known or likely to be resistant (strong recommendation, very low quality evidence). • Amantadine or rimantadine might be administered as chemoprophylaxis against human infection with H5N1 in high or moderate-risk exposure groups if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible (weak recommendation, very low quality evidence). Amantadine or rimantadine should probably not be administered as chemoprophylaxis against human infection with H5N1 virus in low-risk exposure groups if neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible (weak recommendation, very low quality evidence).
Infectious Diseases Society of America/ American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[85]	<u>General recommendations</u> • Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. <u>Empiric therapy - outpatient treatment</u> • For previously healthy patients with no risk factors for drug resistant *Streptococcus pneumoniae* infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant *S pneumoniae*, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate.

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	Empiric therapy - inpatient, non-intensive care unit treatment • A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. • Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. • A respiratory fluoroquinolone should be used for penicillin allergic patients. Empiric therapy - inpatient, intensive care unit treatment • A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. • For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. • For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. • The antipneumococcal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone. • For penicillin-allergic patients, substitute aztreonam for the above β-lactam for *Pseudomonas* infection. Pathogen-directed therapy • *S pneumonia* (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. • *S pneumonia* (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). • *Haemophilus influenza* (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • *H influenza* (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • *Mycoplasma pneumonia/Chlamydia pneumonia*- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. • *Legionella* species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. • *Chlamydia psittaci*- tetracycline preferred; alternative agent is a macrolide. • *Coxiella burnetii*- tetracycline preferred; alternative agent is a macrolide. • *Francisella tularensis*- doxycycline preferred; alternative agents include gentamicin or streptomycin. • *Yersinia pestis*- streptomycin, gentamicin recommended; alternative agents include doxycycline or fluoroquinolone. • *Bacillus anthracis* (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam

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	if susceptible. • *Enterobacteriaceae*- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone. • *Pseudomonas aeruginosa*- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. • *Burkholderia pseudomallei*- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). • *Acinetobacter* species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin. • *Staphylococcus aureus* (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. • *S aureus* (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. • *Bordetella pertussis*- macrolide preferred; alternative agent is SMX/TMP. • Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem. • Influenza virus- oseltamivir or zanamivir preferred. • *Mycobacterium tuberculosis*- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. • *Coccidioides* species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. • *Histoplasmosis*- itraconazole preferred; alternative agent is amphotericin B. • *Blastomycosis*- itraconazole preferred; alternative agent is amphotericin B. • Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting *S pneumonia* and *S aureus.*
American Academy of Neurology Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)**[86]	• Patients with Parkinson's disease (PD), who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and activities of daily living disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the

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	lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
American Academy of Neurology Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[87]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to adverse events and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off-time. • Amantadine is possibly effective in reducing dyskinesia and has demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
American Academy of Neurology: Practice Parameter: **Neuroprotective Strategies and Alternative Therapies for Parkinson Disease (an Evidence-based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology (2006)**[88]	<u>Therapies that can slow the progression of PD</u> • Neuroprotection has the potential to delay the decline of motor symptoms and preserve quality of life. • Currently, the measurement of neurons can only be done postmortem; therefore, surrogate clinical markers (e.g., ratings of motor impairment, general disability, quality of life measures, time to a specific event such as delay for the initiation of symptomatic therapy; motor fluctuation or death) that are thought to reflect nigrostriatal neuron counts need to be employed. Because none of the surrogate markers have been validated, cautious interpretation of clinical trials is required. • Treatment with 2,000 units of vitamin E should not be considered for neuroprotection. • There is insufficient evidence to support or refute the use of the following agents for neuroprotection: riluzole, coenzyme Q10, pramipexole, ropinirole, rasagiline, amantadine or thalamotomy. • Levodopa may be considered for initial treatment (nine months) as it does not accelerate disease progression and is safe; however, there is no long term evidence to recommend its use for neuroprotection. • There is insufficient evidence to recommend the use of selegiline for neuroprotection. <u>Nonstandard pharmacologic or nonpharmacologic therapies that have been</u>

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	shown to improve motor function in PD • Use of complementary medication and treatment is common in patients with PD. • There is insufficient evidence to support or refute the use of *Mucuna pruriens* for the treatment of motor symptoms. • Vitamin E (2,000 units) should not be considered for symptomatic treatment. • There is insufficient evidence to support or refute the use of acupuncture in PD. • There is insufficient evidence to support or refute the use of the following therapies for the treatment of PD: manual therapy, biofeedback and Alexander technique. • Exercise therapy may be considered to improve function. • Speech therapy may be considered to improve speech volume in patients with PD complicated by dysarthria.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2011)**[89]	• No adequate clinical trial has provided definitive evidence for pharmacological neuroprotection or disease modifying effect. • Initiation of treatment is recommended when signs and symptoms begin to have an impact on patient quality of life. • When determining therapy, factors relating to the drug, patient and environment should be taken into account. • Symptom control and the prevention of motor complications are the main issues to consider when determining therapy. • In the management of early untreated PD, monoamine oxidases-B inhibitors (i.e., rasagiline and selegiline) have a modest benefit in treating the symptomatic complications of PD compared to levodopa and (probably) dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration) and are well tolerated (especially rasagiline). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief. • Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • In the prevention of motor complications the early use of controlled-release levodopa is not effective. • Pramipexole and ropinirole (immediate or controlled release) are effective dopamine agonists as monotherapy in the treatment of early PD. • Convincing evidence that older agents in the class are less effective than the newer non-ergot agents in managing patients with early PD is lacking. • Dopamine agonists have a lower risk of developing motor complications. These agents do have a smaller effect on symptoms and a greater incidence of adverse events which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor

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	complications. • Due to the risk of fibrotic reactions ergot derivatives (i.e., bromocriptine, cabergoline and pergolide) are not recommended as first line medications. • The benefits of the early combination of low doses of a dopamine agonist with low doses of levodopa have not been appropriately documented. • A recommendation cannot be made concerning the efficacy of physical therapy and speech therapy in early PD due to a lack of evidence. • Therapy adjustments for patients on dopamine agonist therapy include: o Increase dopamine agonist dose. o Switch to another dopamine agonist. o Add levodopa. • Therapy adjustments for patients on dopamine agonist therapy include: o Increase levodopa dose. o Add a dopamine agonist (efficacy has not been sufficiently evaluated). o Add a catechol-o-methyltransferase inhibitor if motor symptoms evolve (older and multi-morbid patients of any age preferred). • For the treatment of tremor at rest the following are treatment options: o Anticholinergics (possibly useful). o Clozapine (routine use not recommended due to safety concerns). o Beta-blockers (may be effective). o Deep brain stimulation.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2011)**[90]	<u>Symptomatic control of wearing-off</u> • Adjusting the levodopa dose by increasing the dosing frequency (to four to six daily doses) may attenuate wearing off. • Adding a catechol-o-methyltransferase-inhibitor or a monoamine oxidases-B inhibitor as they are effective in reducing off-time by one to 1.5 hours/day. A recommendation cannot be mad as to which agent should be utilized first. However tolcapone is only recommended for patients who fail all other available agents due to safety concerns with the agent. • Adding a dopamine agonist. All dopamine agonists are equally effective and efficacious in reducing off-time. While non-ergot dopamine agonists are first-line compounds, pergolide and other ergot derivatives are reserved for second-line use, due to the adverse events of valvulopathy. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms and this formulation is useful in the treatment of night time akinesia. • Addition of amantadine or anticholinergics may improve symptoms in some cases and should be considered in patients with severe off symptoms who fail the recommended strategies listed above. <u>Symptomatic control of dyskinesias</u> • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of monoamine oxidases-B inhibitors or catechol-o-methyltransferase inhibitors can help control dyskinesias,

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	however the risk of worsening off-time increases. • Patients may benefit for up to eight months by adding amantadine 200 to 400 mg/day for the treatment of dyskinesias. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse events of agranulocytosis limits its use. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias. • Intrajejunal levodopa infusion may be beneficial in patients with marked peak dose dyskinesia and motor fluctuations. <u>Symptomatic control of off-period and early morning dystonias</u> • In cases of off-period dystonia usual strategies for wearing off can be applied. • For the control of dystonia appearing during the night or early in the morning, additional doses of levodopa or dopamine agonist therapy may be effective. • Deep brain stimulation of the subthalamic nucleus may be used for off-period and early morning dystonias. • In both off-period and early morning dystonia botulinum toxin can be employed. <u>Treatment of dementia in PD</u> • Most recommendations are off-label. • Discontinue potential aggravators (i.e., anticholinergics, amantadine, tricyclic antidepressants, tolterodine and oxybutynin and benzodiazepines). • Add cholinesterase inhibitors (i.e., rivastigmine, donepezil, galantamine). Tacrine is not recommended due to associated hepatotoxicity. An alternative agent should be tried prior to abandoning. • If cholinesterase inhibitors not tolerated or lacking efficacy, add or substitute with memantine. <u>Treatment of psychosis in PD</u> • Control triggering factors (i.e., infections, metabolic disorders, electrolyte imbalances, sleep disorders). • Reduce polypharmacy. • Reduce anti-PD agents. • The addition of an atypical antipsychotic has shown to be beneficial. Clozapine's adverse event of agranulocytosis limits its use. Quetiapine is thought to be relatively safe and possibly useful; however, sufficient data does not exist. Olanzapine and risperidone are not recommended. • Typical antipsychotics should not be used as they worsen Parkinsonism. • Add cholinesterase inhibitors (i.e., rivastigmine, donepezil). <u>Treatment of depression in PD</u> • Optimize antiparkinson therapy. • Initiate tricyclic antidepressants.

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	• Compared to tricyclic antidepressants selective serotonin reuptake inhibitors are less likely to produce adverse events. • No recommendations can be made concerning "new" antidepressants (i.e., mirtazapine, reboxetine, venlafaxine). Treatment of orthostatic hypotension in PD • Aggravating factors should be avoided (i.e., large meals, alcohol, caffeine at night, warm environment exposure, volume depletion, drugs known to cause orthostatic hypotension). Drugs that are known to cause orthostatic hypotension include: diuretics, antihypertensive agents, tricyclic antidepressants, nitrates, alpha blockers, levodopa, dopamine agonists, and monoamine oxidases-B inhibitors. • In symptomatic orthostatic hypotension increase salt intake (1 g per meal). • Head up, tilt the bed at night (30 to 40º), may be helpful. • Wear wait high elastic stockings and/or abdominal binders. • Exercise as tolerated. • Maneuvers to prolong patient upright should be introduced (i.e., leg crossing, toe raising, thigh contraction, bending at waist). • For drug therapy, midodrine is the preferred option. The addition of fludrocortisone is a secondary option as it is possibly effective. Treatment of urinary disturbances in PD • An urologist should be referenced to for PD patients with bladder problems, at least if response to anticholinergic therapy is insufficient or if intolerance is present. • Intake after 6 PM should be reduced for the management of nocturia. • Night time dopaminergic therapy should be optimized. • Anticholinergic agents should be utilized with priority given to agents that do not pass the blood-brain barrier. • The efficacy of botulinum was demonstrated in a pilot study with a small sample size. Symptomatic control of dysphagia in PD • A priority should be given to optimization of motor symptoms. In some patients levodopa and apomorphine can improve dysphagia. • Early referral to speech therapist for assessment, swallowing advice and further instrumental investigations if needed. • In selected cases, video fluoroscopy to exclude silent aspiration. • Enteral feeding options may need to be considered. • There is still very limited experience with the following therapies and cannot generally be recommended: surgical therapies, rehabilitative treatments and botulinum toxin. Symptomatic control of gastric dysfunction • In PD gastric emptying is often delayed. • Domperidone can be considered to accelerate gastric emptying. • Transdermal patches may be considered for patients with severe fluctuations in gastric emptying. Symptomatic control of nausea and vomiting • Droperidol is effective and ondansetron may be used as a second line

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	agent. No other antiemetic is recommended. Symptomatic control of constipation • In PD patients constipation is the most commonly reported gastrointestinal symptom. • Anticholinergics should be discontinued as they may worsen constipation. • Increased fluid and fiber intake are recommended. • Increased physical activity may be beneficial. • Polyethylene glycol solution is the preferred therapeutic option with alternative agents being fiber supplements such as psyllium or methylcellulose and osmotic laxatives. • Irritant laxatives should be reserved for selected patients and short duration of treatment. Treatment of erectile dysfunction • Erectile dysfunction is more common in PD patients compared to matched controls. • Agents that are associated with erectile dysfunction should be discontinued. • A positive and negative effect on symptoms may be seen with dopaminergic therapy. • Sildenafil as well as tadalafil and vardenafil may be tried. • Apomorphine injections and intracavernous injections papaverine or alprostadil may be considered in select patients. Treatment of daytime somnolence and sudden onset of sleep • Nocturnal sleep disturbances should be assessed. • Disturbances should be reduced to optimize nocturnal sleep. • Driving should be stopped. • Medications prescribed for other medical conditions should be decreased or discontinued. • The dose of dopaminergic agents should be decreased as they may induce daytime somnolence. • Switch the dopamine agonist to another dopamine agonist. • Add modafinil. • Add other wake-promoting agents (i.e., methylphenidate). Treatment of rapid eye movement sleep behavior disorder • Protective measures such as safeguarding the bedroom should be employed to prevent sleep related injuries. • Antidepressants, specifically selective serotonin reuptake inhibitors should be reduced or withdrawn. • Clozapine may be added at bedtime. Treatment of sleep problems • A standard or slow-release dose of levodopa should be added at bed time. • The following agents improve sleep quality in patients with advanced PD with motor fluctuations: transdermal rotigotine, pramipexole and prolonged release ropinirole. • With the exception of nocturnal motor phenomena of sleep disorders

Clinical Guideline	Recommendation(s)
	deep brain stimulation improves sleep quality in patients with advanced PD.
National Institute for Health and Clinical Excellence: **Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2011)**[91]	• There is no universal first-choice therapy for patients with PD. Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if the patient fails therapy or adverse events prevent titration. • Monoamine oxidase-B inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric adverse events. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in patients with late stage PD, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if adverse events prevent titration. • Monoamine oxidase-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-o-methyl transferase inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.

Conclusions

The two antiviral medication classes available for the treatment and prevention of influenza are the neuraminidase inhibitors and the adamantanes. The neuraminidase inhibitors, oseltamivir and zanamivir, have activity against both influenza A and B. Oseltamivir is Food and Drug Administration-approved for the treatment of influenza in patients two weeks of age and older, and zanamivir may be used in persons seven years of age and older. For influenza prophylaxis oseltamivir is approved for use in persons one year of age and older, while zanamivir is approved for prophylaxis in persons five years of age and older.[3,4] The adamantanes, amantadine and rimantadine, are known to have activity against only influenza A. Both agents are approved for the prophylaxis and treatment of influenza A.[9,10] Specifically, rimantadine is approved for treatment of influenza A in patients 17 years of age or older and for prophylaxis of influenza A in adults and pediatric patients five years of age and older.[9,10] Amantadine and rimantadine are similar in their antiviral activity and older clinical trial results have shown that they provide a similar treatment benefit. Both agents are currently available generically. When used for the treatment of influenza A within the first two days of illness, both amantadine and rimantadine have been shown to be effective in reducing the duration of illness; however, comparative trials between the agents are limited. Amantadine is also approved for the treatment of Parkinsonism and drug-induced extrapyramidal reaction.[12] National guidelines state that amantadine may be used but the evidence of efficacy is not strong indicating that amantadine is not a first-line agent.[87-91] Amantadine is less effective than levodopa in the treatment of Parkinson's disease; however, it has fewer extrapyramidal reactions compared to anticholinergic antiparkinson drugs.[7]

The Centers for Disease Control and Prevention-Advisory Committee on Immunization Practices (CDC-ACIP) as well as the American Academy of Pediatrics and the World Health Organization have developed guidelines and recommendations for prevention and control of influenza. Although annual vaccination is the primary strategy for preventing complications of influenza infections, antiviral medications with activity against influenza may be effective for the chemoprophylaxis and treatment of influenza.[15,82,] These medications should be used in specific situations such as (1) to reduce the spread of influenza to high risk individuals during outbreaks, (2) as chemoprophylaxis during the peak influenza season for unvaccinated individuals who have frequent contact with high risk patients, and (3) individuals at high risk who are expected to have an inadequate antibody response to the influenza vaccine.[15,82,84] Treatment outcomes are most efficacious when antiviral medications are initiated within 48 hours of symptom onset.[15,82,84] Clinicians should administer oseltamivir treatment as soon as possible in patients with confirmed or strongly suspected H5N1 and H1N1 Avian influenza, as well as those who are at high risk of contracting the virus.[15,84] This includes children, elderly, immunosuppressed patients or those with co-morbidities, pregnant women, patients ≤18 years of age receiving long-term aspirin therapy, American Indians/Alaska Natives, morbidly obese patients, nursing home residents, health care personnel, family members who are not immunized and are likely to have close contact with those at high risk, and those who may be in close contact with someone infected with the virus.[15,84] The adamantanes are currently not recommended for treatment or prophylaxis of any strain of influenza due to increasing resistance.[15,82,84]

Clinical study results demonstrate that these agents are effective compared to placebo in reducing the burden of illness, with minimal adverse events, when used for the treatment of influenza within the first two days of illness; however, head-to-head clinical trials of the two neuraminidase inhibitors are lacking.[6] One study comparing oseltamivir, zanamivir, and combination therapy demonstrated that the concomitant administration of oseltamivir and zanamivir was less effective than oseltamivir monotherapy, and not significantly more effective than zanamivir monotherapy in reducing viral load and time to resolution of illness, as well as increasing the number of patients with alleviation of symptoms.[62] Another trial by Kawai and colleagues comparing oseltamivir to zanamivir for the treatment of influenza A and B showed statistically significant improvement in fever duration and percentage of patients afebrile at 24 and 48 hours after the first dose of the study drug. Patients with influenza B who were treated with zanamivir demonstrated significantly shorter fever duration as well as a larger percentage of afebrile patients at 24 hours or 48 hours compared to patients treated with oseltamivir. Between patients with influenza A and influenza B, no significant difference was found in the percentage of patients afebrile at 24 or 48 hours after the start of zanamivir therapy.[59] Tuna et al found that for overall efficacy, oseltamivir and zanamivir had no significant difference, but temperature normalization was significantly faster in the zanamivir group

(P=0.0157).[60] Other studies have demonstrated that, when administered within two days of illness onset to otherwise healthy adults, oseltamivir and zanamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day compared to placebo. As recommended by the CDC, it is imperative to initiate these agents within 48 hours of the onset of symptoms to ensure the efficacy of these agents.

Clinical trials have demonstrated that amantadine and rimantadine are also effective in both the prophylaxis and treatment of influenza A; however, due to a marked increase in resistant isolates, the ACIP recommends that adamantanes not be used in the United States for the treatment of influenza, except in selected circumstances.[1,16,17,23-26,30,32,58,61,67,69-71] Trials have demonstrated an initial decrease in the viral load of those patients treated with rimantadine, but over time the rimantadine treated patients consistently and increasingly shed influenza virus. Additionally, patients treated with rimantadine had a higher percentage of resistant isolates compared to those receiving acetaminophen alone.[61]

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