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Antiviral Drugs for Influenza

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Antiviral Drugs for Influenza

Influenza is generally a self-limited illness, but pneumonia, respiratory failure, and death can occur. FDA-approved antiviral drugs for influenza are listed in Table 2. The neuraminidase inhibitors oseltamivir (Tamiflu, and generics), which is taken orally, and zanamivir (Relenza), which is inhaled, are approved for prophylaxis and treatment of acute uncomplicated influenza. The IV neuraminidase inhibitor peramivir (Rapivab) and the oral polymerase acidic (PA) endonuclease inhibitor baloxavir marboxil (Xofluza) are approved only for treatment.1,2 All of these drugs are active against both influenza A and influenza B viruses. Updated information on influenza activity and antiviral resistance is available from the CDC at www.cdc.gov/flu.

INDICATIONS FOR TREATMENT — Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza infection who is hospitalized, has severe, complicated, or progressive illness, or is at high risk for influenza complications (see Table 1).3-5 False negative results can occur with some influenza tests; patients with suspected influenza infection who have severe, complicated, or progressive illness or are at high risk for influenza complications should receive antiviral treatment despite a negative test result, especially when influenza is known to be circulating in the community.6

Antiviral treatment can be considered for previously healthy persons with suspected or confirmed influenza who are not at high risk for influenza complications if it can be started within 48 hours of illness onset.

Table 1: Patients at High Risk for Influenza Complications

- Children <5 years old (children <2 years old are at highest risk)
- Patients <19 years old receiving long-term treatment with aspirin or salicylate-containing drugs
- Adults ≥65 years old
- Extremely obese patients (BMI ≥40)
- Women who are pregnant or ≤2 weeks postpartum
- Persons of American Indian or Alaska Native heritage
- Residents of nursing homes or other chronic care facilities
- Patients who are immunosuppressed or have chronic medical conditions

PROPHYLAXIS — Antiviral prophylaxis is recommended to help control institutional influenza outbreaks. It can be considered after exposure for persons at high risk for complications who have not received influenza vaccine this season, received it within the previous 2 weeks, or are unlikely to have responded to vaccination, such as those who are immunosuppressed. Prophylaxis is not recommended for healthy persons exposed to influenza or when >48 hours have elapsed since exposure.3

EFFECTIVENESS — Treatment — Use of a neuraminidase inhibitor or baloxavir for treatment of acute uncomplicated influenza in adults shortens the duration of symptoms by about a day.7-9 A meta-analysis of randomized trials in children with influenza found that starting treatment with oseltamivir within 48 hours of symptom onset reduced illness duration by about 18 hours (by 30 hours when trials that enrolled only children with asthma were excluded) and reduced the risk of developing otitis media.10 Although most...
controlled trials of these drugs have not been powered to assess their efficacy in preventing serious influenza complications, experts have generally interpreted the combined results of controlled trials, observational studies, and meta-analyses as showing that early antiviral treatment of influenza in high-risk patients can reduce the risk of complications.  

In clinical trials in healthy outpatients $\geq 12$ years old with uncomplicated influenza, administration of baloxavir within 48 hours of symptom onset shortened the duration of influenza symptoms by about a day compared to placebo; the time to alleviation of symptoms was about the same with baloxavir and oseltamivir.  

Similar results were reported in a trial...
in patients at high risk for influenza complications.\textsuperscript{14} No controlled trials are available on use of baloxavir for treatment of influenza in immunocompromised or hospitalized patients, or in those with severe influenza.

**Prophylaxis** — Neuraminidase inhibitors have generally been about 70-90\% effective when used for prophylaxis against susceptible strains of influenza A or B viruses.\textsuperscript{3} In one trial (BLOCKSTONE; available only as a press release), a single dose of baloxavir was effective when used for prophylaxis, but it is not approved by the FDA for such use.

**TIMING** — **Treatment** — Neuraminidase inhibitors are most effective when started within 48 hours of illness onset, but complications of influenza can occur >48 hours after illness onset. The results of some observational studies in hospitalized and critically ill patients suggest that treatment started as late as 4-5 days after illness onset can reduce the risk of complications such as pneumonia, respiratory failure, and death.\textsuperscript{15-17} Adults (outpatient or hospitalized) with community-acquired pneumonia (CAP) who test positive for influenza should receive antiviral treatment regardless of the duration of illness.\textsuperscript{18} No data are available on the efficacy of baloxavir started >48 hours after symptom onset.

**Prophylaxis** — When indicated, prophylaxis with oseltamivir or zanamivir should be started within 48 hours after exposure to the influenza virus and continued for 7 days after the last known exposure. For institutional outbreaks, the CDC recommends prophylaxis be given for at least 2 weeks and continued for up to 1 week after the end of the outbreak.

**PREGNANCY AND LACTATION** — Pregnant women are at increased risk for severe complications of influenza, including death. Oseltamivir and zanamivir appear to be safe for use during pregnancy.\textsuperscript{19,20} Prompt treatment with oseltamivir is recommended for women with suspected or confirmed influenza who are pregnant or ≤2 weeks postpartum.\textsuperscript{21-23} Oseltamivir, which is minimally excreted in breast milk, is also preferred for treatment of women who are breastfeeding. No data are available on use of baloxavir during pregnancy or while breastfeeding.

Antiviral prophylaxis can be considered for pregnant women who have had close contact with someone likely to have been infected with influenza. Zanamivir may be preferred for prophylaxis because of its limited systemic absorption, but oseltamivir is a reasonable alternative, especially in women at increased risk for respiratory problems.

**RESISTANCE** — Nearly all (>99\%) of the recently circulating influenza virus strains tested by the World Health Organization (WHO) have been susceptible to neuraminidase inhibitors.\textsuperscript{24} Reduced susceptibility of some influenza strains, particularly influenza A(H1N1), to oseltamivir or peramivir can emerge during or after treatment, especially in immunocompromised patients with prolonged viral shedding and in young children.\textsuperscript{25-28} Resistant isolates have usually remained susceptible to zanamivir, but reduced susceptibility to zanamivir has been reported.\textsuperscript{29,30} In immunocompromised patients, use of a double dose of oseltamivir reduced the incidence of oseltamivir resistance compared to standard dosing, but it can cause more adverse effects.\textsuperscript{31}

Baloxavir is active against neuraminidase inhibitor-resistant strains of influenza A and B viruses, including A(H1N1), A(H5N1), and A(H3N2). Amino acid substitutions associated with reduced susceptibility to baloxavir have occurred following treatment with a single dose.\textsuperscript{3} Reduced susceptibility to baloxavir appears to be more frequent in influenza A(H3N2) viruses and in children, and person-to-person transmission of resistant strains may occur.\textsuperscript{32,33} Baloxavir is not recommended for severely immuno-suppressed patients because of concerns that prolonged replication of the influenza virus in these patients could lead to emergence of resistance. Oseltamivir and peramivir may be active against influenza strains with reduced susceptibility to baloxavir.\textsuperscript{34}

**ADVERSE EFFECTS** — Nausea, vomiting, and headache are the most common adverse effects of oseltamivir; taking the drug with food may minimize GI adverse effects. Diarrhea, nausea, sinusitis, fever, and arthralgia have been reported with zanamivir. Inhalation of zanamivir can cause bronchospasm; the drug should not be used in patients with underlying airway disease. Diarrhea and neutropenia have occurred with peramivir. Neuropsychiatric events, including self-injury and delirium, have been reported in patients taking neuraminidase inhibitors, but a causal relationship has not been established, and neuropsychiatric dysfunction can be a complication of influenza illness.\textsuperscript{35}

Baloxavir was well tolerated in clinical trials. It appears to cause less nausea and vomiting than oseltamivir.\textsuperscript{2}

**DRUG INTERACTIONS** — Use of a neuraminidase inhibitor or baloxavir within 48 hours before or ≤2 weeks after administration of the intranasal live-
attenuated influenza vaccine (Flumist Quadrivalent) could inhibit replication of the virus, reducing the vaccine’s efficacy.

Coadministration of antacids, laxatives, multivitamins, or other products containing polyvalent cations such as calcium, aluminum, iron, magnesium, selenium, or zinc can reduce serum concentrations of baloxavir and should be avoided.


32. E Takashita et al. Influenza A(H3N2) virus exhibiting reduced susceptibility to baloxavir due to a polymerase acidic subunit 138T substitution detected from a hospitalized child without prior baloxavir treatment, Japan, January 2019. Euro Surveill 2019; 24:pii=1900170.
34. M Seki et al. Adult influenza A (H3N2) with reduced susceptibility to baloxavir or peramivir cured after switching anti-influenza agents. ID Cases 2019; 18:e00650.