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FREQUENTLY ASKED QUESTIONS

(ARCHIVED) Antiviral Medications for Seasonal Influenza: Information for Health Care Providers, 2019

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What are antiviral medications for influenza?

Antiviral drugs currently used in Canada for the treatment and prevention of seasonal influenza are oseltamivir (Tamiflu®), which is administered orally and zanamavir (Relenza®), which is inhaled. Peramivir (Rapivab®) is available only for treatment in adults and is administered intravenously. Amantadine is an older antiviral medication that is no longer used because circulating strains have developed resistance to it.

Oseltamivir, zanamivir and peramivir are neuraminidase inhibitors, which work by blocking the exit of the influenza virus from respiratory cells and therefore prevent further replication of the virus. Because of this mechanism of action, they should be taken as soon as possible, ideally within 48 hours of symptom onset, when used for treatment.

What are the recommendations for the use of influenza antiviral medications?

Influenza antiviral medications are recommended for:

- Treatment in both outpatient and inpatient settings of those at high risk for complications of influenza, such as adults 65 years of age and over, pregnant women and women up to four weeks post-partum, Indigenous people and those with underlying medical conditions (see Appendix A for additional details)
- Treatment of moderate, progressive, severe or complicated influenza, such as individuals who are hospitalized with influenza-like illness
- Treatment and prevention in influenza outbreaks in institutional settings (see How are antiviral medications used in institutional influenza outbreaks?)[1]

When influenza is circulating, laboratory confirmation of influenza is not needed before initiating treatment in order to avoid delays in starting therapy.[2] Although treatment is generally more beneficial if given early, it can still be considered in those at high risk for influenza complications if more than 48 hours has passed from symptom onset. Treatment is recommended, regardless of time from symptom onset, in individuals with moderate, progressive, severe or complicated influenza-like illness, such as individuals who are hospitalized with influenza-like illness.

If patients without risk factors for complications and without serious illness present within 48 hours of symptom onset, antiviral treatment can be used as follows: on a case-by-case basis for those less than 1 year of age; can be considered, but is not routinely recommended, for those 1 to 5 years of age; and can be considered in those 18 to 64 years of age.[1]

How can health care providers determine if influenza is circulating?

Public Health Ontario posts a weekly Ontario Respiratory Pathogen Bulletin, which provides information about the circulation of influenza and other respiratory pathogens in Ontario. There is an overall influenza activity assessment based on several provincial indicators and information is also available by public health unit jurisdiction, as there can be regional variation in influenza activity. In addition, public health units provide information about local influenza activity and some produce their own surveillance reports.

How are influenza antiviral medications used?

The following table describes key features related to the use of oseltamivir and zanamivir. Additional details can be found in the product monographs and AMMI Canada Guidelines: Use of Antiviral Drugs for Seasonal Influenza: Foundation Document for Practitioners – Update 2019. For use of peramivir, see the product monograph.

	Oseltamivir	Zanamivir (5 mg per inhalation)
Dosage for treatment	75 mg twice daily for five days for adults. See AMMI guideline[a] for pediatric dosing. Dose adjustments may be needed if person is known to have renal impairment. See AMMI guidelines.[b]	10 mg (two inhalations) twice daily (approximately 12 hours apart) for five days.[c] Note that zanamivir is not generally recommended for residents in longterm care facility outbreaks.
Dosage for prevention	For adults, 75 mg once daily for 10 days or in an outbreak, until the outbreak is declared over. See AMMI guideline[a] for pediatric dosing. Dose adjustments may be needed if person is known to have renal impairment. See AMMI guidelines.[b]	10 mg (two inhalations) once daily for 10 days or in an outbreak, until the outbreak is declared over. Note that zanamivir is not generally recommended for residents in longterm care facility outbreaks.
Age authorized for use	One year of age and over. Can be considered on a case-by-case basis for those younger than one year of age.[a]	Seven years of age and over.
Side effects	Nausea, vomiting, headache.[d] Taking with food may increase tolerability. Post-marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese children).[d] See product monographs for additional details.	Allergic-like reactions: oropharyngeal or facial edema, bronchospasm, especially in those with underlying airway disease; sinusitis; dizziness.[d] Post-marketing reports of serious skin reactions, and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese children).[d] See product monograph for additional details.
Contraindications	None[d] See product monographs for additional details.	Underlying respiratory conditions, such as chronic obstructive pulmonary disease or asthma. Allergy to milk protein.[d]
	Oseltamivir	**Zanamivir (5 mg per inhalation)**
		See product monograph for additional details.
Product monographs	Oseltamivir product monographs	Relenza® product monograph

a. For pediatric dosing, see Table 2 of the AMMI Canada Guidelines: Use of Antiviral Drugs for Seasonal Influenza: Foundation Document for Practitioners – Update 2019.

b. Checking creatinine clearance and dose adjustments are not required for those who are not known to have renal impairment. For those with *known* renal impairment, alternative dosing based on creatinine clearance is provided in Table 3 of the AMMI Canada Guidelines: Use of Antiviral Drugs for Seasonal Influenza: Foundation Document for Practitioners – Update 2019.

c. A second dose (10 mg, which is two inhalations) should be taken on the first day of treatment whenever possible, provided there is at least two hours between the initial dose and the second dose (based on the product monograph for Relenza®).

d. For more information, see CDC Influenza Antiviral Medications: Summary for Clinicians.

Is influenza antiviral resistance a concern?

Prior to the emergence of the A(H1N1) pandemic in 2009, almost all circulating A(H1N1) strains in 2008–2009 were resistant to oseltamivir, but sensitive to zanamivir;[3] however, there is very little resistance to oseltamivir or zanamivir among recently circulating strains of influenza. Influenza strains are regularly monitored for antiviral resistance with results provided for Ontario in the Ontario Respiratory Pathogen Bulletin and nationally in Canada's FluWatch reports.

How are antiviral medications used in institutional influenza outbreaks?

When an influenza outbreak is declared in an institutional setting, antiviral medications are recommended for:

- Treatment of ill residents/patients meeting the case definition, regardless of immunization status
- Prophylaxis of residents/patients who are not ill with influenza symptoms and are located within the outbreak area, regardless of immunization status
- Prophylaxis of unvaccinated staff members
- Prophylaxis of vaccinated staff members when there is a mismatch between the vaccine and circulating influenza strains, based on consultation with public health officials[4]

Antiviral medications for treatment and prophylaxis should begin as soon as possible in an outbreak. Rapid initiation of antivirals for prophylaxis is very important in limiting the spread of influenza in an outbreak. Details on planning for the rapid initiation of antiviral medications are provided on pages 49 and 50 of the Control of Respiratory Infection Outbreaks in Long-Term Care Homes, 2018. For influenza outbreaks in long-term care homes, oseltamivir is the preferred antiviral medication for residents, as it is administered orally. For prevention, antiviral drugs should be used for the duration of the outbreak.

Information on prophylaxis following treatment can be found on page 55 of the document entitled Control of Respiratory Infection Outbreaks in Long-Term Care Homes, 2018.[4]

What is the evidence regarding the effectiveness of antiviral medications?

The following briefly describes some studies that provide summary estimates of the effectiveness of antiviral medication in reducing the duration of influenza symptoms and complications and in preventing influenza.

DURATION OF SYMPTOMS

When oseltamivir is used for treatment, it decreases the duration of symptoms by:

- Almost 17 hours in adults (16.8 hour reduction; 95% confidence interval (CI): 8.4 to 25.1) and 29 hours in otherwise healthy children without asthma (95% CI: 12 to 47) based on a meta-analysis of data from randomized trials collected by Jefferson et al. in 2013.[5]

- Approximately one day (25.2 hour reduction; 95% CI: 16.0 to 36.2) in a meta-analysis by Dobson et al. using patient-level data from published and unpublished randomized trials where oseltamivir was given to adults with laboratory-confirmed influenza within 36 hours of illness onset. Data was searched up to November 27, 2014.[6]

- Over 17 hours (17.6 hour reduction; 95% CI: 0.7 to 34.5) in a meta-analysis by Malosh et al. using patient-level data from published and unpublished randomized trials for children less than 18 years of age with laboratory-confirmed influenza where oseltamivir was administered within 48 hours of symptom onset. The meta-analysis used articles published between January 1, 1997 and May 1, 2016.[7]

Results similar to the studies above were found for oseltamivir and zanamivir in a systematic review and meta-analysis of observational studies by Hsu et al. based on published and unpublished studies up to November 2010[8] and in a systematic review of systematic reviews and/or meta-analyses of randomized trials and observational studies of neuraminidase inhibitors conducted by Doll et al. based on searching the published literature between January 1, 1995 and November 10, 2015.[9]

COMPLICATIONS

Meta-analyses of randomized controlled trials have assessed the impact of oseltamivir on influenza complications:

- Jefferson et al. did not find an effect of oseltamivir on influenza-related complications,[5] which may be due to the enrollment of mostly healthy individuals who often do not develop complications from influenza.[10]

- Dobson et al. noted a 44% reduction (risk ratio (RR) = 0.56; 95% CI: 0.42 to 0.75) in the risk of lower respiratory tract complications requiring antibiotics more than 48 hours after randomization and a 63% reduction (RR = 0.37; 95% CI: 0.17 to 0.81) in hospital admission for any cause for those infected individuals receiving oseltamivir within 36 hours of symptom onset compared to those who did not receive oseltamivir.[6]

- Malosh et al. found a 34% reduction in otitis media in children with laboratory-confirmed influenza when oseltamivir was administered within 48 hours of onset of symptoms (RR = 0.66; 95% CI: 0.47 to 0.95) compared to those without treatment; the impact on lower respiratory tract infections occurring more than 48 hours after initiating therapy was not statistically significant (RR= 0.75; 95% CI: 0.37 to 1.52).[7]

META-ANALYSES OF OBSERVATIONAL STUDIES HAVE ALSO SHOWN THE BENEFITS OF NEURAMINIDASE INHIBITORS:

- A meta-analysis by Muthuri et al. of individual-level data of hospitalized patients with laboratoryconfirmed or clinical pandemic influenza (A/H1N1pdm09) in 2009–2010 showed a 19% decrease in the risk of death (adjusted odds ratio (OR) = 0.81; 95% CI: 0.70 to 0.93) when patients were given neuraminidase inhibitors compared to those who were not treated. Early treatment (within two days of symptom onset) showed increased benefit with a risk reduction in mortality of 50% (adjusted OR = 0.50; 95% CI: 0.37 to 0.67) compared to no treatment. More benefit was seen in persons 16 years of age and over (25% reduction; OR = 0.75; 95% CI: 0.64 to 0.87) than in children younger than 16 years of age (18% reduction; OR = 0.82; 95% CI: 0.58 to 1.17).[11]

- Venkatesan et al. assessed individual-level data for pandemic A/H1N1pdm09 influenza in 2009–2010 (91.4% of patients were laboratory-confirmed) to determine if outpatient treatment with a neuraminidase inhibitor decreased the risk of hospitalization (the treatment needed to have started at least the day before hospitalization). In the adjusted analysis, the risk of hospitalization was decreased by 76% (adjusted OR = 0.24; 95% CI: 0.20 to 0.30) with oseltamivir treatment compared to no treatment.[12]

- In their qualitative synthesis and meta-analysis of observational studies that assessed mortality from pandemic A/H1N1pdm09 influenza, Heneghan et al. found insufficient evidence to demonstrate an effect of oseltamivir treatment. A meta-analysis of studies with individual patient data found insufficient evidence of a reduction in risk of mortality with oseltamivir treatment (hazard ratio = 1.03, 95% CI: 0.64 to 1.65) after adjusting for potential confounders and biases.[13]

- In their meta-analyses of observational studies published prior to November 2010, Hsu et al. found the following adjusted estimates comparing oseltamivir treatment to no treatment: a 77% reduction in mortality among hospitalized patients (OR = 0.23; 95% CI: 0.13 to 0.43); a 25% reduction in hospitalization among outpatients (OR = 0.75; 95% CI: 0.66 to 0.89); a non-significant reduction in pneumonia (OR = 0.83; 95% CI: 0.59 to 1.16); a 25% reduction in otitis media (OR = 0.75; 95% CI: 0.64 to 0.87); and a 42% non-significant reduction in any recurrent cardiovascular events (OR = 0.58; 95% CI: 0.31 to 1.10).[8]

PROPHYLAXIS

Influenza antiviral medications are very effective when used for prophylaxis in reducing symptomatic influenza.

- The review by Jefferson et al. found that oseltamivir prophylaxis reduced symptomatic influenza by 55% compared to placebo (RR = 0.45, 95% CI: 0.30 to 0.67).[5]

- A meta-analysis by Okoli et al. that assessed individual level protection of pre- and post-exposure oseltamivir found it to be 89% effective (OR = 0.11; 95% CI: 0.06 to 0.20) at preventing laboratoryconfirmed influenza. The search was done up to December 2012 and included randomized controlled trials and observational studies.[14]

- The systematic review of systematic reviews and/or meta-analyses by Doll et al. found that oseltamivir or zanimivir were consistently associated with a decrease in odds/risk of symptomatic secondary transmission by 50 to 90% (OR/RR range 0.1 to 0.5) when used either for pre-exposure or post-exposure prophylaxis.[9]

Which organizations recommend influenza antiviral medications?

Antiviral medications are recommended by a number of organizations, including the following:

1. **Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada)**

Use of Antiviral Drugs for Seasonal Influenza: Foundation Document for Practitioners – Update 2019 provides treatment, prophylaxis and outbreak management recommendations with regard to influenza antiviral medications.[1]

2. **Ontario Ministry of Health**

Control of Respiratory Infection Outbreaks in Long-Term Care Homes, 2018 provides guidance regarding the treatment and prophylaxis of residents of long-term care facilities during influenza outbreaks and also regarding prophylaxis of staff members of these facilities during influenza outbreaks.[4]

3. **Canadian Paediatric Society (CPS)**

The Use of Antiviral Drugs for Influenza: Guidance for Practitioners (2018) provides antiviral treatment recommendations for the Canadian pediatric population.[15]

4. **Centers for Disease Control and Prevention (CDC)**

The CDC website entitled, Antiviral Drugs: Information for Health Care Providers,[16] provides a comprehensive overview of the use of influenza antiviral medications, including a document entitled, Influenza Antiviral Medications: Summary for Clinicians.

5. **Infectious Diseases Society of America (IDSA)**

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza provides recommendations regarding treatment and prophylaxis of influenza using antiviral medications.[17]

6. **European Centre for Disease Prevention and Control (ECDC)**

Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza – review of recent systematic reviews and meta-analyses provides evidence that supports the use of neuraminidase inhibitors for the treatment and prevention of influenza. It concluded that neuraminidase inhibitors are a reasonable public health measure during seasonal influenza outbreaks, pandemic and zoonotic outbreaks for susceptible strains of influenza.[18]

For additional information, please contact your local public health unit or Public Health Ontario by phone or email at cd@oahpp.ca.

Appendix A

List of conditions that increase the risk for influenza complications:

- chronic pulmonary disease, including asthma
- cardiovascular disease (excluding hypertension)
- malignancy
- chronic renal insufficiency
- diabetes mellitus and other metabolic disease
- anemia and hemoglobinopathies, such as sickle cell disease
- immunosuppression due to disease or medication
- neurologic and neurodevelopmental disorders
- children younger than 5 years of age (although for children without other risk factors and without serious illness, antiviral medications are only used if the patient presents within 48 hours of symptom onset as follows: on a case-by-case basis for those less than 1 year of age; and can be considered, but are not routinely recommended, for those 1 to 5 years of age)
- individuals 65 years of age or older
- people of any age who live in nursing homes or other chronic care facilities
- pregnant women and up to 4 weeks post-partum
- individuals < 18 years of age who are on chronic aspirin therapy, due to the risk of Reye's syndrome related to influenza
- morbid obesity (body mass index ≥ 40)
- Indigenous peoples

Sources for list of conditions that increase the risk of influenza complications:

- Canadian Immunization Guide. Chapter on influenza and statement on seasonal influenza vaccine for 2019–2020:[19] List 1

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