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Health Management Bulletin

OTC ANALGESICS

Education Modules for Physicians

Because the array of available OTC analgesics is likely to create confusion among patients, physicians may be called upon to offer advice on these products, and to consider whether an OTC or a prescription medication is warranted.

Over-the-Counter Analgesics in Cold and Influenza

In the course of a year, upper respiratory tract infections or "colds" are almost inevitable—it is estimated that the average adult experiences 2 to 4 colds a year, and children, 4 to 10. Although most colds are self-limited, it is estimated that colds account for about 40% of all time lost from jobs, and about 30% of the absenteeism from school.[1] While influenza is less common, local epidemics can result in significant morbidity and mortality, particularly among older patients and those at high-risk who have not been immunized. About 10,000 to 20,000 people in the United States die each year from the flu or its complications, and approximately 1 of every 100 people who get the flu require hospitalization, particularly older and chronically ill patients. Yearly influenza immunizations have been recognized as a high priority by the Centers for Disease Control and Prevention.

The ubiquity of colds and flu have spawned some 800 different over-the-counter (OTC) products containing various combinations of analgesics, decongestants, antihistamines, antitussives, or expectorants—open any medicine cabinet in the United States, and you are likely to find several different products. It is estimated that every year Americans spend $1.5 to $2 billion for these products.[1,2] The array of available products is likely to create confusion among patients who may have a difficult time determining the combination of ingredients appropriate (or not) for their particular set of symptoms. Physicians may be called upon to offer advice on these OTC products, and additionally, physicians must carefully consider

whether prescription medications are warranted, particularly antibiotics. This Health Management Bulletin will review the pathophysiology and treatment of colds and flu, with a focus on OTC preparations.

The Viruses

While the symptoms of colds and flu may overlap, colds are typically distinguished by fatigue, sneezing, coughing, and coryza—without high fever. Colds due to rhinoviruses can occur at any time during the year (see Figure 1). In contrast, influenza (ie, flu) is seasonal and is characterized by the abrupt onset of fever, malaise, anorexia, weakness, myalgias, headache, cough and coryza. The severity of symptoms and the presence of a high fever may distinguish colds from flu. During a flu epidemic, up to 40% of people living in a given community may develop the flu over a several week period.

Because of the increased incidence of both colds and flu during the winter, a commonly held notion is that cold exposure and chilling will cause a cold. This is not the case. In fact, the patterns of illness coincide with those times when people are more apt to be crowded together indoors, either due to inclement weather or children congregating in school classrooms. The important factor in the spread of colds and flu is proximity to an infected individual; for colds, spreading most commonly occurs by direct contact, while flu is most commonly spread through aerosolized droplets.

Colds

Colds are caused by a wide variety of viruses; rhinovirus is the most common, accounting for about 30% of colds. Coronavirus, parainfluenza and respiratory syncytial viruses are responsible for a large percentage of the remaining colds. Table 1 summarizes the viruses causing common colds by age group.

Although all cold viruses can cause disease throughout the year, many have characteristic patterns of occurrence, as noted in Figure 1.

There are approximately 100 different subtypes of rhinovirus, a small, single-stranded RNA virus. The number of subtypes and the structure of the virus itself, make vaccination for

Table 1. Viruses Causing Common Cold by Age Group

	Younger than Age 4	5-10 Years Old	Adolescents	Young Adults	Older Adults
Most Common	Rhinovirus	Parainfluenza	Rhinovirus	Rhinovirus	Rhinovirus
	RSV	Adenovirus	Influenza	Echovirus	Influenza
	Parainfluenza	Enterovirus	Echovirus	Influenza	Echoviruses
	Adenovirus	RSV	Coronaviruses	Coxsackievirus	Coxsackievirus
	Influenza	Rhinovirus	RSV	Coronaviruses	Coronaviruses
		Influenza	Parainfluenza	RSV	RSV
			Adenovirus	Parainfluenza	Parainfluenza
Least Common				Adenovirus	Adenovirus

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rhinovirus unlikely. The predominant symptoms of rhinovirus are headache, cough, and malaise, although lower respiratory and gastrointestinal symptoms may also be present. The illness is maximal for 2-3 days, and persists on average for about 7 days. Complications of rhinovirus—or any cold virus—include bacterial sinusitis and otitis media, presumably secondary to obstruction of the eustachian tube or sinus orifice due to swelling. Additionally, patients with asthma and bronchitis may experience an acute exacerbation of their underlying disease.

Coronaviruses, another common single-stranded RNA virus, produce a pattern of infection similar to rhinoviruses. Many strains of coronaviruses cannot be cultured, and thus, their incidence in populations cannot be precisely measured; however, they are thought to be a common cause of colds. During times of peak infection in the winter and spring, coronaviruses may be responsible for as many as 35% of colds. Parainfluenza virus, a member of the *Paramyxoviridae* family (another single-stranded RNA virus), is related to measles, mumps and respiratory syncytial viruses (RSV). These viruses are more commonly seen in association with lower respiratory symptoms. For example, some strains of parainfluenza and respiratory syncytial viruses are common causes of croup and bronchiolitis in young children. In particular, RSV is a major cause of lower respiratory illness in young children, which eclipses its role as a cause of the common cold.

Adenoviruses, which are double-stranded DNA viruses, can also cause the common cold and are characterized by mild pharyngitis or tracheitis. Adenovirus is also responsible for pharyngoconjunctival fever, characterized by conjunctivitis, pharyngitis, rhinitis, cervical adenopathy

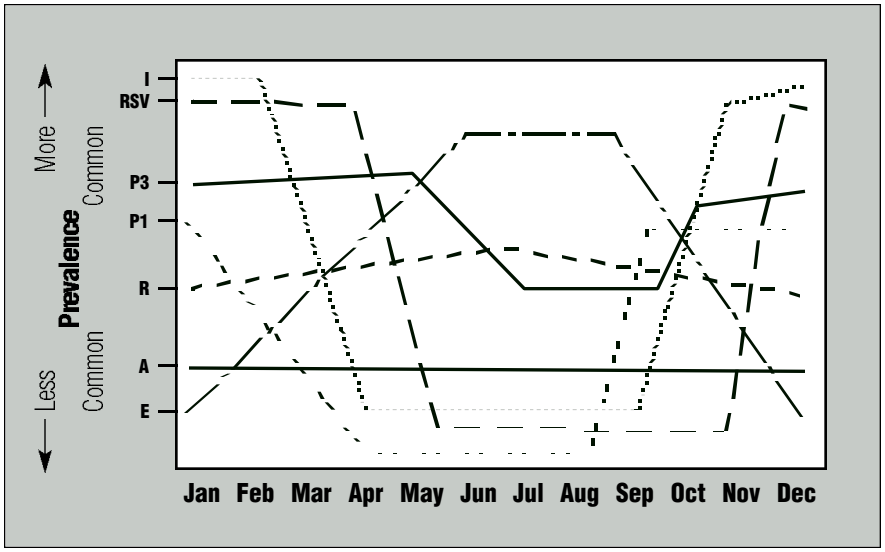

Figure 1. Seasonal prevalence of common cold viruses. I=influenza; RSV = respiratory syncytial virus; P3 = parainfluenza type 3; P1 = parainfluenza type 1; R = rhinovirus; A = adenovirus; E = enterovirus. Reprinted with permission from Kirkpatrick GL.[1]

and mildly elevated temperature. Most common in the summer, adenovirus frequently occurs in small outbreaks, typically at a summer camp.[3]

In clinical practice, it is rarely necessary to identify the specific pathogen, due to the self-limited nature of the disease and the lack of treatment specific to any given virus.

Influenza

The threat of a pandemic, and the morbidity and mortality of flu epidemics, have made surveillance and an annual program of immunization for high-risk patients a significant public health priority. The morbidity of flu is, in part, related to its complications: bacterial sinusitis, otitis media, and exacerbations of underlying diseases, such as asthma, chronic obstructive pulmonary disease and congestive heart failure. Pneumonia, in the form of primary viral pneumonia or secondary bacterial pneumonia, is also a serious complication.

Annual flu epidemics are distinct from the uncommon, and potentially devastating, pandemics, on the basis of the immunology and antigenicity of the particular etiologic influenza A and B viruses. Influenza A viruses are classified into subtypes on the basis of two surface antigens (HA and NA); three subtypes of hemagglutinin (HA); and two subtypes of neuraminidase (NA). Immunity to one subtype provides no protection to other subtypes. In addition, both influenza A and B are subject to antigenic drift, a process of naturally occurring mutation; consequently, immunity to one strain may not protect against a similar, related strain that may emerge in subsequent years. Annual epidemics of flu are largely the result of antigenic drift; distinct strains of influenza A and B viruses may emerge every 2 to 5 years.[4] Antigenic drift provides the rationale for an annual flu shot to prevent disease. Every year, the Centers for Disease Control and Prevention recommends the antigenic make-up for flu shots, consisting of three virus strains (two influenza A and one influenza B), that are likely to circulate in the United States in the upcoming winter. Therefore, the effectiveness of the vaccine will vary, depending on the similarity between the virus strain in the vaccine and those that

eventually circulate. Good matches can prevent illness in 70%-90% of otherwise healthy individuals, and can prevent hospitalizations in 30%-70% of elderly community dwellers and in 50%-60% of individuals living in nursing homes.

In contrast, the more ominous pandemics result from antigenic shifts, in which certain animal influenza A viruses, normally found only in birds or swine, are transmitted to humans. Due to the total lack of immunity, a pandemic can be a truly devastating event. The "Spanish" flu epidemic, which began in 1918, was thought to be responsible for 20 million deaths—far exceeding the number who died in the preceding World War. Pandemics are thought to arise in China, where human, avian and swine populations closely coexist.[5] Therefore, the World Health Organization (WHO), in conjunction with other public health organizations, has established a program of global surveillance for these viruses.[6]

■ Treatment

Colds

Treatment of the common cold can be best described as palliative, and the lack of an effective treatment for this common ailment is frustrating. Clinical data on the efficacy of common cold medications are limited for several reasons, including the absence of well-designed clinical trials and the subjective nature of most outcome measures. The common symptoms of colds (eg, congestion; rhinorrhea; coryza; cough; myalgias; and fever–predominantly in children), can be eased with a variety of single or combination OTC preparations. When considering whether to recommend a single agent or combination product for cold symptoms, it is important to note that while the majority of patients experience most of the symptoms of a cold, not all these symptoms occur at the same time.[7] Individualized, single-drug therapy permits the use of effective doses of appropriate drugs to treat specific symptoms, without exposing the patient to unnecessary treatment. Further, the effectiveness of some components of cold medications has been questioned. All patients should be adequately educated about the strengths and limitations of OTC preparations. An overview of common cold medications used singly or in combination is provided in the following sections.

- **Analgesics**

OTC analgesics include 2 basic categories: acetaminophen, and aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen, aspirin and other NSAIDs are antipyretics, as well as analgesics, and can treat the cold-associated fever, as well as the headache and myalgias. Aspirin is contraindicated in children because of its association with Reye's syndrome; otherwise, the choice of antipyretic/analgesic agent is largely empiric. The American Lung Association recommends acetaminophen as the drug of choice, with an analgesic and antipyretic action equivalent to NSAIDs, and a favorable safety profile.[9] Patients should be warned about combining single ingredient analgesics with other cough and cold preparations that may contain another or the same analgesic, leading to doses that exceed the recommended levels. In addition, patients should be asked if they regularly consume alcohol-containing beverages ($\geq$ 3 drinks daily), before recommending acetaminophen or NSAIDs.

- **Antihistamines**

Antihistamines (eg, chlorpheniramine, diphenhydramine, pheniramine, tripolidine) have been recommended as a treatment of rhinorrhea or sneezing, originally based on their effectiveness in treating the rhinorrhea associated with allergic rhinitis. However, it is not clear that common cold viruses prompt the release of histamines, and the effect of antihistamines may be more related to their anticholinergic action. Consequently, newer generation antihistamines without anticholinergic actions, such as terfenadine, may not be effective.

Controlled clinical trials have reported conflicting results for antihistamine effectiveness in different populations. One review concluded that antihistamines offer only a marginal benefit, if any.[1] Another study randomized 688 volunteers with colds to receive either an antihistamine (doxylamine succinate) or a placebo; the treatment group reported a small, but statistically significant improvement in rhinorrhea and sneezing compared to the control group.[10] In contrast, Clemens and colleagues reported disappointing results using a decongestant and antihistamine combination in preschool children.[11] The only benefit appeared to be drowsiness, which benefited those children with cold-induced sleep deprivation. However, drowsiness, no matter how appreciated by parents, must be balanced by the other side effects of antihistamines, including paradoxical excitability and dizziness. In addition, respiratory depression and hallucinations may occur when the recommended dose of antihistamines is exceeded. For patients with asthma, antihistamines may be contraindicated because of their effect in drying airway secretions.

- **Decongestants**

Alpha-adrenergic agonists cause vasoconstriction of the nasal mucosa and thus, are potent decongestants that have long been used in the treatment of common colds. Oxymetazoline is available as a nasal spray. Ephedrine, phenylpropanolamine, phenylephrine and pseudoephedrine are available orally. While effective, these agents are associated with side effects, such as

increased blood pressure, elevated pulse rate, fatigue and dizziness. They should be used cautiously in patients with hypertension; those with labile or difficult to control hypertension are at greatest risk. Patients with other cardiovascular diseases, diabetes mellitus, or benign prostatic hypertrophy, should also use these drugs cautiously. In addition, overuse of topical nasal decongestants can lead to rebound nasal congestion, prompting a vicious cycle of drug use.

- **Expectorants**

Guaifenesin is the most common OTC expectorant, intended to reduce sputum viscosity and thus, facilitate removal of tracheobronchial secretions. However, controlled clinical trials have failed to validate its effectiveness.[12]

- **Antitussives**

The most common OTC antitussive is dextromethorphan, which is thought to function by suppressing cough through a central action on the medullary cough center. In a review of clinical trials of OTC cold medications published between 1950-1991, no studies were identified that permitted objective assessment of the antitussives.[12] Menthol rubs, also marketed for their antitussive properties, are thought to act through the local anesthetic action of the aromatic vapors.

- **Topical Anesthetics**

Lozenges, gargles, and sprays containing topical anesthetics and antiseptics are extensively marketed to patients. Products containing local anesthetics may be used every 3 to 4 hours and may provide temporary symptomatic relief. Antiseptics have no role in the treatment or prevention of viral upper respiratory tract infections.

- **Zinc Lozenges**

The use of zinc lozenges in the treatment of colds remains controversial. At least 8 randomized controlled clinical trials have been published, with half reporting positive results and the other half reporting negative results. The reported trials have typically focused on adults. Most recently, Macknin and colleagues conducted a randomized trial of zinc lozenges to treat cold symptoms in children.[13] Children in the treatment group were instructed to take 10 mg zinc lozenges, 5 times per day; there was no significant impact on cold symptoms. The discrepancy in results among the trials could be related to the preparation of zinc, which could affect its bioavailability; the dosage used; appropriate masking of the unpleasant taste of zinc to prevent a "treatment effect" unrelated to any (potential) pharmacologic effect; small sample sizes; and limitations in data analysis. The mechanism of action of zinc is also unclear. Theories include the inhibition of rhinovirus replication, interference of viral binding to an intercellular adhesion molecule, or modulation of nerve endings of the trigeminal or facial nerve, resulting in a reduction of nasal symptoms.[14] Advocates of zinc lozenges stress that lozenges should be taken within 24 hours of the onset of symptoms, and that adequate doses are required.[15] For example, in one randomized study, the recommended dosage was 13.3 mg of zinc every waking hour.[16] The palatability and frequency of dosing may limit adherence outside of clinical trials.

- **Vitamin C**

The role of vitamin C in the treatment of colds has been touted since 1971 when Linus Pauling published a meta-analysis that concluded vitamin C could reduce cold-related symptoms. A 1975 review by Chalmers came to the opposite conclusion, and others supported his interpretation.[17] The controversy continues, with recent reviews challenging Chalmers' assessment; the addition of newer studies to the analyses led one author to conclude that vitamin C significantly decreases the duration and severity of colds by an average of 23%.[18] Doses in the range of 1 gm/day may be required.

- **Heated Vapor**

While not an OTC drug, heated vapor is a frequently recommended home remedy. Inhalation of heated (or unheated) humidified air may sooth irritated airways and improve airway hydration. In addition, raising the temperature of the nasal mucosa is thought to inhibit the replication of rhinovirus. However, recent studies have failed to show any beneficial effects on cold symptoms. A study which randomized 68 volunteers with colds to receive a one-hour steam treatment of 40L/min of heated air, or a control group which received a one-hour treatment of ambient air at 2L/min, showed no significant difference in the daily symptoms between the two groups.[19] In a study of subjects experimentally infected with rhinovirus, no significant difference in the amount of viral shedding was found between the group receiving two intranasal steam treatments and the controls, casting doubt on the underlying rationale for heated vapor treatment of colds.[20]

- **Prescription Medications**

Intranasal Ipratropium Bromide

Intranasal ipratropium is an anticholinergic agent without systemic side effects, which has been used to treat rhinorrhea. However, the side effect of nasal drying may limit its use. In a trial which randomized 411 patients to receive ipratropium bromide nasal spray, buffered salt nasal spray, or no treatment, the primary outcomes included subjective and objective measures of rhinorrhea and assessment of the patient's overall perception of well-being.[21] The

authors found that the ipratropium provided both subjective and objective relief of rhinorrhea. However, the differences between the treatment and control groups, although statistically significant, were relatively modest, due in part to a placebo effect in the control groups. There was no difference in nasal congestion among the groups. The treatment was well-tolerated, but there was a higher incidence of blood-tinged mucus and nasal dryness in the ipratropium treated group.

Antibiotics

Antibiotics should be reserved for cold-related complications, such as sinusitis and otitis. However, the emergence of antibiotic-resistant bacteria is, in part, related to the excessive, often inappropriate use of antibiotics in ambulatory medicine. Although the overwhelming majority of colds are caused by viruses, several articles have documented the overuse of antibiotics in the treatment of uncomplicated common cold. For example, in a cross-sectional sample of Kentucky Medicaid claims for the common cold, 60% reported a prescription for an antibiotic.[22] Extrapolating their results to the overall incidence of colds, the authors conservatively estimate that this inappropriate use of antibiotics adds some $37 million annually to the health care budget. Gonzales and colleagues reported on antibiotic use as part of the 1992 National Ambulatory Medical Care Survey.[23] A total of 51% of patients diagnosed as having colds, and 52% of patients diagnosed with upper respiratory tract infections, received prescriptions for antibiotics. The authors found overuse of antibiotics across geographic areas, medical specialties and payment sources. The overuse of antibiotics may be highest in the United States. In a study of Dutch physicians, it was reported that antibiotics were prescribed in only 17% of cases of upper respiratory tract infections.[24]

Patient expectations have been cited as one reason for this apparent overuse.[22, 25] For example, patients whose symptoms have warranted a physician office visit may be dissatisfied when no curative option is offered. However, this perception may be mistaken. In a survey of 73 office visits for the common cold, it was found that there was no relationship between patient satisfaction and receipt of a prescription, advice to take OTC products, or simple self-care advice.[25] Many patients sought physician advice merely to rule out a more serious disease. Support for the theory that patient expectations influence prescription writing comes from a survey of pediatric office visits for cough; these authors found that when the physician perceived the parent expected a prescription medication, a prescription was more likely to be given.[26]

■ Influenza

The strengths and limitations of OTC preparations are similar for symptomatic treatment of the flu. However, management of the flu focuses on prevention—specifically, immunization of those at high-risk for its complications. The CDC has identified the following patients either at high-risk for the flu, or at high-risk of transmitting the flu to vulnerable patients.[27] It is recommended that all of the following patients receive annual influenza immunizations:

At-risk patients

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

The recommendation for immunization of certain pregnant women is new, and is based on reports that pregnancy may increase the risk for serious medical complications of the flu. The MMWR cites studies reporting increased hospitalization rates for women in the second and third trimester of pregnancy during flu season; researchers estimated that a program of prenatal vaccination could prevent 1 to 2 hospitalizations for every 1,000 pregnant women vaccinated.[27]

Groups that can transmit influenza to persons at high-risk

- Physicians, nurses, and other personnel in both hospital and outpatient-care settings.
- Employees of nursing homes and chronic-care facilities who have contact with patients or residents.

- Providers of home care to persons at high-risk (eg, visiting nurses and volunteer workers).
- Household members (including children) of persons in high-risk groups.

Groups that should not be vaccinated

- Persons known to have anaphylactic hypersensitivity to eggs, or other components of the virus.
- Adults with acute febrile illnesses.

Every year during the month of September, the vaccine for the upcoming influenza season becomes available; the optimal time for vaccination extends from October through mid-November, since the peak influenza season occurs between late December and early March.

From a low vaccination rate of only 25% in 1987, rates have increased steadily. In 1993, it was estimated that 50%-55% of patients over the age of 65 were vaccinated; however, it is still estimated that almost 25 million high-risk individuals remain unvaccinated.[28] Some individuals may not seek out vaccination due to concerns regarding their side effects. In 1976, there was considerable publicity regarding the putative complication of Guillain-Barre syndrome in those receiving vaccinations for the swine flu. However, subsequent analysis has failed to confirm a causal relationship. Patients should be reassured that vaccinations do not contain infectious viruses, and thus, cannot cause influenza. However, fever, malaise and other systemic symptoms can occur following vaccination, and are most often seen in small children who have had no previous exposure to influenza.

■ Treatment

Two antiviral agents, amantadine and rimantadine, can be used either as prophylaxis or as therapy. As prophylaxis in non-immunized high-risk patients, the CDC recommends that these drugs must be taken every day for the duration of peak influenza activity in the community. Patients can still be vaccinated during peak influenza activity, but due to the delay in development of immunity, these high-risk patients should receive chemoprophylaxis with either amantadine or rimantadine for at least two weeks.[27] Prophylaxis may also be considered for non-immunized persons providing care to those at high-risk, for patients with immune deficiency, and for patients in whom the vaccine is contraindicated (eg, those with severe allergies to eggs). As therapy, amantadine and rimantidine have been found to be effective in reducing the morbidity and mortality of influenza, if initiated within 48 hours of illness onset.

The basic treatment for most patients is symptomatic. The patient should be instructed to remain in bed or rest adequately, and avoid exertion during the acute stage and for 1 to 2 days after their temperature returns to normal. Symptoms of acute, uncomplicated influenza may be treated with antipyretics/analgesics (eg, for adults, acetaminophen or aspirin).[29] The American Lung Association recommends acetaminophen to relieve the discomfort (eg, muscle aches, sore throat, fever, chills) associated with influenza infections. A nasal decongestant may be considered to relieve nasal congestion. Steam inhalation may be helpful in relieving respiratory symptoms and in preventing drying of nasal secretions.

■ Summary

Treatment of colds and flu are a significant component of primary care physicians' office practice. As such, physicians should become familiar with the strengths and limitations of the ubiquitous OTC preparations. Overuse of antibiotics has been widely documented in the treatment of colds and flu, and physicians should consider their appropriateness carefully and never use them routinely. Finally, influenza vaccination of high-risk patients has been identified as a high public health priority; physicians need to identify high-risk patients and educate them about the importance of vaccination.

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Address all correspondence to:
R. Mark Evans, PhD
American Medical Association
Healthcare Education Products and Standards
515 North State Street
Chicago, IL 60610
mark_evans@ama-assn.org