

Rationale for Treatment of Common Cold and Flu with Multi-Ingredient Combination Products for Multi-Symptom Relief in Adults

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Abstract

This up-to-date overview will look at the rationale for the recommendation of combination products for multi-symptom relief of common cold and flu. Common cold and flu are defined by their multi-symptom nature with data showing a variety of symptoms reported simultaneously each day over the first six days of illness. Multi-ingredient combination products for multi-symptom relief are formulated to safely, simply, and simultaneously treat multiple symptoms when used as directed. The rationale for the formulation combination products for common cold and flu is therefore practical, logical and reasonable. No evidence has been found that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. Multi-symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of common cold and flu, when used as directed. This therapy requires some special information for the patient to be provided by the physician and the pharmacist.

Keywords

Combination Products, Multi-Symptom Relief, Multi-Ingredient, Common Cold, Flu

1. Introduction

Acute upper respiratory tract viral infections (URTI), often referred to as common cold and flu, are the most

common diseases of humans with adults suffering from 2 - 5 common colds each year and school-children suffering from 7 - 10 colds each year [1]. It accounts for up to 40% of sick leaves among US employees [2] and for 10% of the 1.3 billion annual outpatients and emergency department visits in the US [3]. In general there are 1 billion such patients per year in the US [4]. The symptoms of URTI are so common that self-diagnosis of common cold or flu is common amongst the general public, although most in Germany will consult a physician or pharmacist for diagnosis and treatment of this condition. The terms of common cold and flu have been used to describe a common syndrome of symptoms long before the discovery of the viruses responsible for the disease state, and some experts describe the common cold as a “culturally accepted constellation of respiratory symptoms” [5]. This constellation of symptoms makes the common cold and flu unique among common diseases as no other condition has such a range of symptoms that occur simultaneously. Each symptom can be treated with a separate active ingredient, but multi-symptom relief, using combination products with multiple active ingredients is chosen by many pharmacists [6]. This up-to-date overview will look at the rationale for the recommendation of combination products for multi-symptom relief of common cold and flu.

2. Natural History of Cold and Flu

URTI, “common cold” and “flu” are syndromes of familiar symptoms caused by viral infection of the upper respiratory tract that can be caused by any 1 of 200 sera types of virus [7]. It is difficult to exactly define the common cold and flu syndromes because of great variation in the severity, duration and types of symptom. Rhinoviruses account for 30% - 50% of all colds, and corona viruses are the second most common agent accounting for 10% - 15% of colds [8]. Influenza viruses account for much flu-like illness and also 5% - 15% of colds, and colds viruses such as respiratory syncytial virus (RSV) are responsible for much flu-like illness [9], demonstrating that there is much overlap in the etiology and symptomatology of common cold and flu syndromes. In terms of common knowledge, the common cold is considered a mild illness with symptoms usually restricted to the nose and throat (a head cold), whereas flu is perceived as a more severe systemic illness with fever and muscle aches accompanying the common cold symptoms [10]. Flu-like illness and common cold may be caused by common cold viruses and by influenza viruses, but if one refers to “influenza” it is best to reserve this term for verified infection with an influenza virus. The severity of symptoms with influenza may vary from an asymptomatic sub-clinical infection up to a disabling feverish illness that may also involve lower respiratory tract infection [11] leading to laryngotracheobronchitis, bronchiolitis and pneumonia [12].

3. Common Cold and Flu Are a Multi-Symptom Disease

A URTI may commence with a single symptom such as a scratchy dry irritating sensation in the throat but after a period of usually a day it develops to include other symptoms such as runny nose, sneezing, sore throat, dysphonia, headache, blocked nose or nasal congestion, cough, sinus pain, watery eyes, loss of appetite, muscle aches and pains, chilliness, low-grade fever, sleep problems and malaise [13]. A combination of several symptoms usually persists for the duration of the illness over a week or more. Not all of the above symptoms may occur in every case of URTI but by definition and in diagnosis, the common cold and flu are multi-symptom syndromes with a constellation of symptoms [5] [14]. The multi-symptom nature of common cold and flu has been highlighted in a recent review where the timeline of the illness indicates that up to eight symptoms may occur over the same period [15]. Any one symptom occurring in isolation would not be diagnosed by the patient or clinician as a common cold or flu. Throat or nasopharyngeal irritation is one of the first signs of URTI, but if this symptom develops into a sore throat without any other accompanying symptoms it is more likely to be diagnosed and named as a sore throat, nasopharyngitis, pharyngitis, tonsillitis or laryngitis rather than be termed a common cold [16] [17]. Similarly, the presence of a fever, muscle aches, sleep problems or a cough as isolated symptoms would not lead to a diagnosis of a flu-like illness or influenza [18]. The WHO guidelines for registration of fixed-dose combination medicinal products states that if a fixed-dose-combination medicine is intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate [19]. Clinical studies using experimentally induced colds as well as studies of naturally occurring colds demonstrate the development of simultaneous multiple symptoms in patients suffering URTI. The first attempt to define the common cold as clinical entity was made by Jackson *et al.* in 1958 who experimentally infected over 1000 students with nasal washings taken from patients diagnosed with a common cold [20]. The aim of the

study was to determine the symptom complex that defined a common cold on the basis of symptom scores for eight symptoms, sneezing, headache, malaise, chilliness, nasal discharge, nasal obstruction, sore throat, and cough. The study clearly demonstrated that over a six day period of observation most of the symptoms were present in any one patient with a cold, and that multiple symptoms were present simultaneously. The multi-symptom nature of common cold is illustrated in **Figure 1** which graphs the development of six selected common cold symptoms over a six day period in 209 volunteers who developed colds after being challenged with nasal washing containing a common cold virus, based on the results of Jackson *et al.* (1958) [20]. The figure clearly shows that on every day over the six days period, all of the six symptoms of sore throat, headache, sneezing, cough, nasal congestion and runny nose were present simultaneously. Severity of each symptom was assessed using a 4-point scale. The figure represents data from all 209 subjects and is expressed as the total symptom score per 100 subjects (*i.e.* as a percent). Not all of the six symptoms would have been present in any one individual on any one day, but the majority of participants would have had multiple symptoms on any one day. The early study on an unidentified virus by Jackson *et al.* (1958) [20] has been followed by many studies using experimental infection with identified common cold viruses. For example, Tyrrell *et al.* (1993) infected volunteers with a range of different viruses (three types of rhinovirus, a respiratory syncytial virus and a corona virus) and found that the common cold symptoms generated by these different viruses were the same, and that multiple symptoms occurred simultaneously in all patients diagnosed as having a cold [21]. A study comparing naturally acquired and induced colds by Turner *et al.* in 1996 also reported the presence of multiple symptoms under both conditions [22]. The development of common cold symptoms in subjects in an industrial population in the USA was studied by Gwaltney *et al.* (1967) [23] over a three year period. The investigators recorded a total of 3314 URTI of which one third (1025) were sampled for virology and 239 of these samples were identified as rhinovirus infections. The subjects were asked to record the presence of symptoms and did not score severity of symptoms as did those in the Jackson *et al.* (1958) [20] study described above. The frequency of occurrence of six symptoms from days 1 - 9 is illustrated in **Figure 2**, which illustrates that all of the six symptoms were present in the population throughout the nine days period with the greatest incidence during the first four days of the illness. **Figure 1** and **Figure 2** are illustrating the multi-symptom nature of URTI have different time courses and peaks for each symptom. The differences between the figures are first because **Figure 1** illustrates the varying severity of the six symptoms whereas **Figure 2** illustrates the varying incidence of each of six symptoms. Secondly the figures are based on different populations, different methods of gathering data, and different viral infections. **Figure 1** relates to viral challenge with an unknown virus whereas **Figure 2** relates to naturally acquired rhinovirus infections. Despite these differences it is clearly apparent from the figures that URTI is characterized as a multi-symptom disease. The multi-symptom nature of common cold and flu means that physi-

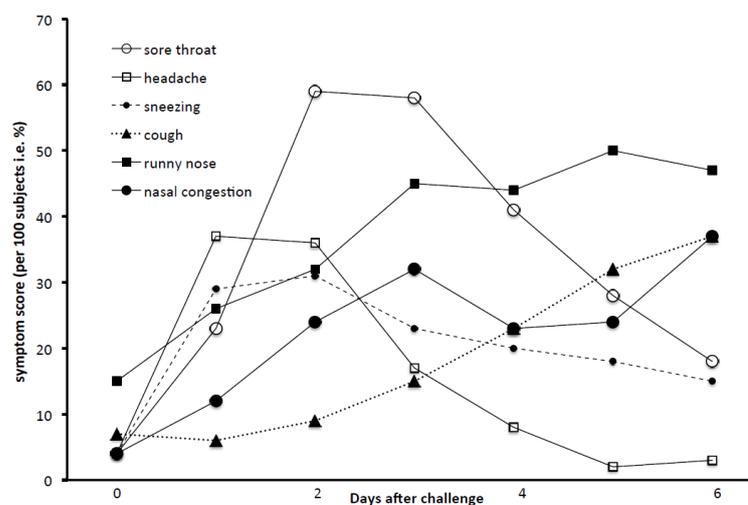


Figure 1. Symptom scores over a six days period after nasal challenge with infected nasal washing taken from a patient with common cold. The figure represents the pooled data from 209 subjects and is expressed as the total symptom score per 100 subjects (*i.e.* percent). The results are redrawn from a study by Jackson *et al.* (1958) [20].

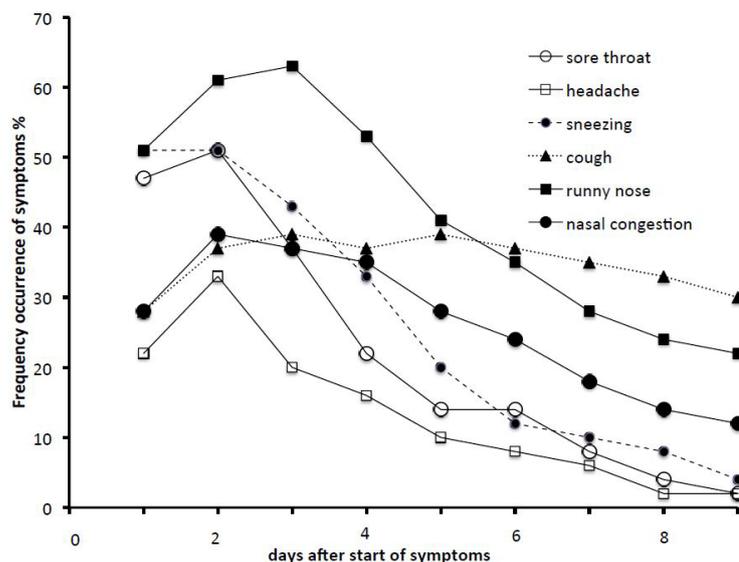


Figure 2. Frequency of occurrence of symptoms expressed as a percentage. Based on 139 subjects diagnosed with rhinovirus infection. Results are expressed as percentage of subjects suffering from the symptom on any one day over a nine day period. The results are redrawn from a study by Gwaltney *et al.* (1967) [23].

cians, pharmacists and patients have several different options for treatment, and when they decide to use a symptomatic treatment they can choose to treat each symptom with a different treatment or choose to use a multi-symptom relief combination medicine. Because of the multi-symptom presentation of common cold, non-prescription that is over-the-counter (OTC), multi-active ingredient medicines have been used for over sixty years for the treatment of colds and flu [24] [25].

3.1. Benefits of Multi-Ingredient Medicines for Multi-Symptom Relief

The safety and efficacy of any medical treatment is first dependent on compliance of the patient to take their medicines as directed, as overdosing might lead to an increased risk of side effects occurring and under-dosing may mean that the treatment is ineffective in treating the disease state. The pharmacist has an important role in instructing the patient on the use of any medicine and particularly non-prescription (OTC) multi-active ingredient medicines, as pharmacists are the only healthcare professionals specifically trained in non-prescription therapeutics, and also trained to ask the patient about symptoms of their condition in order to assess their chief complaint and determine the best course of therapy [6]. The benefits of multi-ingredient therapy have been accepted for treatment of chronic diseases such as hypertension and Parkinsonism and diabetes [26] but there is still some resistance for this type of therapy for acute diseases such as URTI. The rationale for multi-ingredient medicines for treatment of simultaneous multiple symptoms of URTI agrees with that proposed by the WHO Expert Committee Report on fixed-dose combination medicinal products, since there is an identifiable patient group suitable for this type of multi-symptom relief therapy [19]. The WHO Expert Committee Report also states that the larger the identifiable patient group, the more significant is the rationale for combining actives for treatment [19], and this could not be more relevant for a disease as common as URTI.

3.2. Compliance and Ease of Treatment

In any medical treatment it is self-evident that the simpler the dosing regimen the more likely it is that the medicines will be taken in the correct dose at the correct time. If a patient needs to take three different medicines it greatly simplifies the treatment regimen if all the medicines can be taken in a single dose. A meta-analysis of research on how fixed dose combinations affect compliance with a treatment regimen reported that non-compliance to medication decreased by 26% when patients took fixed dose combinations [27]. This meta-analysis

was based on chronic diseases such as hypertension but the concept also applies to acute conditions such as URTI where patients can be confused when dealing with several single ingredient medicines to treat multiple symptoms. A recent workshop on combination therapies involving 48 international researchers and experts representing academia, industry and regulatory authorities reported “The impact of introduction of medicines combinations for more therapies is immense for both patients and for society. While it generally can be argued that little is gained in substituting two small tablets with one big, the major advantages come from the concept of simplifying the overall treatment regimen for the patient” [26]. An important factor with demonstrated effects on compliance is formula convenience. The combination of multiple common cold or flu relief active ingredients in a single dose formula offers the patient the convenience of treating multiple symptoms with a single product and may therefore promote improved compliance to the treatment. This helps support both patient safety and optimal efficacy of the medicines [6] [27].

3.3. Efficacy

The efficacy of any medicine depends on taking the correct dose at the correct times. Under-dosing by missing a dose or taking doses of medicine at extended dose intervals will affect the efficacy of any medicine. The combination of several active ingredients into a single dose ensures that the needed medicines are all taken together. This simple treatment can help improve compliance as discussed above, to ensure the optimal efficacy of the medicines. A benefit of a multiple targeted therapy for the efficacy and/or adherence was shown also for some other medical conditions like breast cancer [28], hypertension [29], hypertension/dyslipidemia [30], HIV [31], duodenal ulcer [32] and multiple migraine attacks [33]. A detailed discussion about the efficacy of symptomatic treatments for common cold and flu is beyond the aims of this review and the reader is directed to reviews such as that in a recent text book on common cold [34]. Because of the large range of products only a few examples demonstrating efficacy of multi-symptom relief cold and flu products can be given in this review. The range of commonly used individual active ingredients and the range of symptoms they are used to treat are shown in **Table 1**. The seven therapeutic categories of active ingredients can be combined in many different ways to formulate multi-symptom relief products. The efficacy of a few combinations of actives that have been tested by high quality clinical trials will be discussed to demonstrate the efficacy of multi symptom relief active ingredient combinations as shown in **Table 2**.

3.4. Dual Combination Medicines

Dual combination treatments are the most common multi-symptom relief medicines. A combination of an analgesic such as paracetamol or acetylsalicylic acid with a decongestant such as pseudoephedrine is a typical multi-symptom relief medicine. A recent study by Eccles & Voelker (2013) illustrates the safety and efficacy of a fixed combination of acetylsalicylic acid and pseudoephedrine for symptomatic relief of pain symptoms and

Table 1. Therapeutic categories of common cold and flu active ingredients and the symptoms they treat.

Medicine category	Active ingredients	Symptoms treated
Analgesic	Aspirin, paracetamol, ibuprofen	Headache, sore throat pain, muscle aches, fever, chilliness, sinus pain, ear ache
Oral decongestant	Pseudoephedrine, ephedrine, phenylephrine	Blocked nose
Topical decongestant	Oxymetazoline, xylometazoline, naphazoline, tramazoline, tryzoline	Blocked nose
First generation antihistamine	Doxylamine, diphenhydramine, chlorpheniramine	Runny nose, sneezing, cough
Antitussive	Dextromethorphan, pholcodine, codeine, pentoxyverine	Dry cough
Expectorant/mucolytic	Guaiphenesin, ambroxol, acetylcysteine, bromhexin	Productive cough
Anticholinergic	Ipratropium, tiotropium	Runny nose

Table 2. Selected examples of multi-symptom relief studies.

Study	Active ingredients	Dose form	Number of patients	Main efficacy outcome measures	Efficacy results
Eccles & Voelker (2013)	Acetylsalicylic acid, pseudoephedrine	Granules dissolved in water to give flavoured drink	833	Subjective scores of pain and objective measure of nasal airflow conductance	Efficacy of combined active ingredients superior to placebo
Eccles <i>et al.</i> (2007)	Xylometazoline, ipratropium	Nasal spray	786	Subjective scores of runny nose and congestion	Efficacy of combined active ingredients superior to placebo
Mizogouchi <i>et al.</i> (2007)	Acetaminophen, doxylamine, succinate, dextromethorphan, ephedrine sulphate	Syrup	485	Composite and individual subjective scores of nasal congestion, runny nose, cough, pain relief	Multi-ingredient symptom scores superior to placebo and also individual symptom scores
Eccles <i>et al.</i> (2006)	Paracetamol, pseudoephedrine	Tablet	305	Subjective scores of pain and objective measure of nasal airflow conductance	Efficacy of combined active ingredients superior to placebo
Loose & Winkel (2003)	Acetylsalicylic acid, pseudoephedrine	Granules dissolved in water and capsules	643	Subjective scores of pain and congestion	Efficacy of combined active ingredients superior to placebo

nasal congestion associated with common cold [35]. The rationale for the treatment is that nasal congestion and pain commonly occur simultaneously and that a combination medicine provides a simplification of therapy compared to use of acetylsalicylic acid and pseudoephedrine as mono-therapies. This study involved 833 patients with common cold and was a randomized double-blind, placebo-controlled, four-arm parallel group study design, involving a single dose of treatment in the clinic and three days treatment at home. The study clearly demonstrated that the combination therapy provided relief for pain symptoms such as headache and sore throat pain and also relief for nasal congestion compared to placebo and mono-therapies. The study also provided further support for the safety of acetylsalicylic acid and pseudoephedrine as common cold symptom relief actives, as there were no unexpected adverse events and no serious adverse events attributed to the study medicines. This study supports the results of a previous clinical trial on a combination of acetylsalicylic acid and pseudoephedrine which demonstrated superiority of each active ingredient above placebo for symptom relief [36]. Similar high quality, randomized, placebo-controlled clinical trials have been performed on dual combination therapies such as paracetamol and pseudoephedrine [37] for treatment of pain and nasal congestion respectively; and ipratropium and xylometazoline for treatment of runny nose and congestion [38].

3.5. Triple and Quadruple Combination Medicines

Active ingredients from the seven categories of medicines in **Table 1** may be combined in various ways according to the perceived needs of patients for multi-symptom relief of common cold or flu symptoms. Triple combinations are commonly marketed with analgesic, first generation antihistamine and nasal decongestant. This triple combination provides some general benefit in adults and older children [39] [40]. It treats symptoms of pain, runny nose, sneezing, and nasal congestion. The first generation antihistamines are commonly used in multi symptom relief medicines as they have a broad pharmacological activity and also act as sedatives, which make them particularly beneficial for night-time treatment of common cold. There is a well known relationship between sleep quality and susceptibility to the common cold [41]. Good sleep is essential for a healthy immunity [42]. Therefore a sleep aid is essential for any inflammation which impairs the sleep quality. Doxylamine is one of the hypnotic compounds which are used widely by patients as an OTC therapy for insomnia [43]. The antihistamine diphenhydramine has been used for over sixty years in multisymptom medicines to control cough [44]. The antihistamines doxylamine and chlorpheniramine have been shown to be effective in relieving sneezing probably by peripheral and central anticholinergic actions [45] [46]. Recently Picon *et al.* (2013) [47] showed that symptomatic treatment of the common cold or flu-like syndrome in adults with a fixed-dose combination of paracetamol, chlorpheniramine and phenylephrine is effective compared to placebo. Seagrave *et al.* (2012) [48] reported on a good efficacy of guaifenesin, N-acetylcysteine, and ambroxol on mucociliary transport in human tracheal-bronchial cells which may be useful treating airway mucus hypersecretion and mucostasis in airway

diseases. The efficacy of triple treatment (ibuprofen, pseudoephedrine and chlorpheniramine) in children with allergic rhinitis, cough and cold is discussed by Fan *et al.* (2013) [49]. As illustrated in **Figure 1** and **Figure 2** the six symptoms of sore throat, headache, sneezing, cough, runny nose, and nasal congestion all occur simultaneously over much of the first 6 days of the cold and may persist for up to 9 days, and therefore multi-symptom relief medicines may contain four or more active ingredients to treat all these symptoms simultaneously. The literature on the efficacy of combinations of four active ingredients is still limited as with each extra ingredient to be tested the complexity of the clinical trial increases. Even when testing a simple dual ingredient combination medicine the study may involve four different arms [35]. **Table 2** includes an example of a four-active ingredient treatment containing ephedrine as a nasal decongestant, the antihistamine doxylamine for treatment of runny nose and sneezing, dextromethorphan for cough suppression and paracetamol for treatment of pain symptoms such as sore throat and headache. With this four-active ingredient medicine all the six different common cold symptoms illustrated in **Figure 1** can be treated simultaneously. Additionally a sleep promoting effect can be assumed by paracetamol and doxylamine. This four-active ingredient medicine formulated as syrup was tested in a double-blind, randomised, placebo-controlled clinical trial involving 545 patients (485 treated) which clearly demonstrated the benefits of each active ingredient above placebo treatment with only minimal adverse events (1%) and no serious adverse events [50].

3.6. Safety

No evidence has been found that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. The active ingredients in multi-symptom relief common cold products each have different mechanisms of action and they do not interact with each other. It is sometimes suggested that with multi-active ingredient common cold medicines the potential toxicity is compounded because they contain several active ingredients [51], but this disregards the basic pharmacology and safety profile of the active ingredients. There is no evidence suggesting compounding of toxicity and if this was the case the medicines would not be licensed for sale to the public. The important issue with any medicine is that it is taken as instructed on the label. In general, medicines for the treatment of common cold symptoms are safe, as they are mass marketed for the general population and taken in millions of doses every day during the common cold season. Any safety issue with common cold medicines will be quickly observed because of the very large population using these medicines. Multi-symptom relief common cold products are not different to respective single-active ingredient products as regards safety, when taken in the labelled doses. Two recently published studies, one by Janin and Monnet (2014) [52] with a fixed-combination syrup containing paracetamol, phenylephrine hydrochloride and guaifenesin and one by Picon *et al.* (2013) [47] with fixed-dose combination of paracetamol, chlorphenamine and phenylephrine reported about a good safety profile and a good tolerance. An important safety debate concerning multi-ingredient, multi-symptom relief products for common cold and flu is that they commonly contain paracetamol (acetaminophen) and that users who may not be aware of this may accidentally overdose when they take the multi-ingredient product with other medicines also containing paracetamol [53]. However, the 2009 FDA meeting and report on the future of acetaminophen in the USA recognized that the main problem of overdose was with single ingredient formulations of acetaminophen and that the percentage of fatalities attributed to non-prescription combination products was less than with acetaminophen alone and acetaminophen/opioid combinations [54]. However the FDA committee did believe that there could be an increase in patient risk with combination products because of lack of patient awareness with regard to the ingredients, and they recommended improved labeling and enhancing the prominence of the word “acetaminophen” on the label.

4. Discussion and Conclusion

Common cold and flu are defined by their multi-symptom nature with data showing a variety of symptoms reported simultaneously each day over the first six days of illness. Multi-ingredient combination products for multi-symptom relief are formulated to safely, simply, and simultaneously treat multiple symptoms when used as directed. The rationale for the formulation combination products for common cold and flu is therefore practical, logical and reasonable. With this multi-ingredient combination, products do have an important place compared to other available therapies, ranging from a mono phytotherapy [55] and traditional Chinese medicine [56] up to antiviral therapy [57]. Multi-ingredient combination therapy should be a first-line treatment, at least if multiple symptoms are found, no bacterial infection is present, and if preventive actions fail such as physical inter-

vention, vaccination or passive immunization. No evidence has been found that multi-ingredient combination products inherently introduce any additional safety risks compared to corresponding single active ingredient products. Multi-symptom relief combination products containing several active ingredients therefore provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of common cold and flu, when used as directed. This therapy requires some special information for the patient to be provided by the physician and the pharmacist. More research for this extremely common health problem is needed. More high-quality clinical trials showing efficacy and safety of multi-ingredient combination products for multi-symptom relief are needed, since physicians and pharmacists recommend these products routinely.

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