

Practical clinical reviews

Treatment of COVID-19 symptoms with over the counter (OTC) medicines used for treatment of common cold and flu

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A B S T R A C T

Persons suffering from acute upper respiratory tract viral infections (URTI) commonly use over the counter (OTC) medicines to relieve symptoms such as fever, muscle aches, cough, runny nose, sore throat and nasal congestion. At present OTC medicines are only licensed for treatment of common cold and flu symptoms and not for treatment of the same symptoms associated with COVID-19. The innate immune response responsible for the mechanisms of the symptoms of URTI is the same for all respiratory viruses including SARS-CoV-2 and these symptoms can be relieved by treatment with the same OTC medicines as available for treatment of colds and flu. This review provides scientific information that OTC treatments for common cold and flu-like illness caused by respiratory viruses are safe and effective treatments for the same symptoms associated with COVID-19.

Introduction

Acute upper respiratory tract viral infections (URTI) are the most common of human infections and are responsible for an enormous burden of disease ranging from a trivial common cold to severe fatal pneumonia (Johnston, 2005; Eccles, 2013; Boncristiani et al., 2009). Although the diseases may be defined by identification of the causative virus, they are more commonly defined by the clinical syndrome such as common cold and flu-like illness. When the infection is limited to the upper respiratory tract the syndromes most often present as an acute mild disease such as a common cold (Wat, 2004), but when the infection reaches the lower respiratory tract the manifestations may be severe and life threatening such as bronchiolitis, pneumonia and exacerbation of asthma (Johnston, 2005). The severity of URTI varies widely, and severe disease is more likely in older adults, infants, and those with underlying medical conditions. This review discusses the respiratory viruses and how they cause symptoms, and makes a case that symptomatic treatments are safe and effective for symptomatic relief of the common cold and flu-like symptoms associated with all respiratory viruses, including SARS-CoV-2.

Search strategy and selection criteria

All the authors are involved in research on respiratory viruses and the proposal for this review article was initiated by RE who was in contact with the other authors (GB, BJC, AP and RS). RE proposed the idea of this review and used his personal database of literature on symptomatic treatments of common cold and flu to outline the paper. The other authors then commented and criticised the outline and used their own databases of literature on respiratory viruses to add content and references to the final paper.

Respiratory viruses

The airway is the most commonly infected area of the body and this is because it is directly exposed to the external environment through inspired air. An adult breathes in 10 000–15 000 L of air a day. A 2-year-old child has a respiratory rate at rest of 26 breaths per minute (Fleming et al., 2011) which equates to 37 000 breaths each day, thus the respiratory tract is continuously exposed to potential infection from large volumes of inspired air. However, the most common respiratory infections are restricted to the upper airways, and “All known respiratory viruses are able to produce the illness complex recognized as the common cold (Johnston, 2005).” The restriction of most common

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respiratory infections to the upper airway is related to the “temperature sensitivity” of respiratory viruses as most human respiratory viruses have evolved to replicate most efficiently at the temperature of the upper airway mucosa (32 °C–35 °C) and this is cooler than the core body temperature found in the lower airways (37 °C) (Eccles, 2021).

The human respiratory viruses comprise ten groups as illustrated in Table 1. The respiratory viruses form a varied group with enveloped and non-enveloped viruses, RNA and DNA viruses but they are all capable of causing mild disease expressed as a common cold syndrome or flu-like illness. The same viruses are also capable of infecting the lower airways and respiratory infectious disease are a major cause of morbidity and mortality, especially in infants and the elderly, and were responsible for more than 3.8 million deaths globally in 2017 (Huang and Guo, 2022; Jain et al., 2015).

Syndromes of upper respiratory tract viral infection

Infection with respiratory viruses exhibit a range of syndromes from asymptomatic and common cold to pneumonia and death, but the most common outcome of viral infections is a mild common cold illness which resolves in a few days as illustrated by the iceberg concept of infection in Fig. 1. The iceberg concept is a fundamental concept in virology (Kaslow et al., 1997). The iceberg concept of viral infection predicts that after asymptomatic infections the next most common syndrome is a mild self-limiting illness like the common cold, with symptoms such as sore throat, runny nose, nasal congestion, cough and sneezing as illustrated in Fig. 1. The concept is illustrated by a study on 214 healthy individuals (age 3–63 years) (Galanti et al., 2019). Nasopharyngeal swabs and symptom scores were taken twice a week for two years. Of 4215 samples collected, 737 were positive for one or multiple respiratory viruses (influenza viruses, respiratory syncytial viruses, human rhinoviruses, coronaviruses, adenoviruses, parainfluenza viruses, human metapneumovirus) and amongst the positive results, 69%–74% of the samples were classified as asymptomatic. In another study 2,685 participants were recruited from among visitors to a New York City tourist attraction over two seasons, and depending on the definition of ‘asymptomatic’, 65–97% of URTI were classified as asymptomatic (Birger et al., 2018). Another study looking at weekly symptom scores and viral detection of 16 respiratory viruses over a period of one year in 108 subjects aged 1 day–57 years in Utah USA reported that 46% of

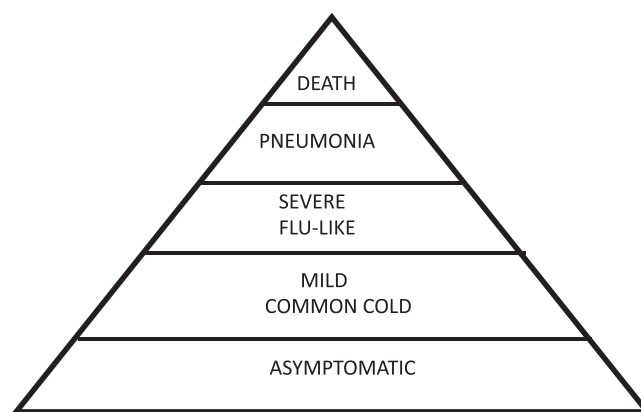


Fig. 1. Iceberg concept of viral infection. Most common outcome of infection is asymptomatic. A mild common cold like illness is the next most common syndrome of illness, followed by less common severe illness such as pneumonia, with the tip of the iceberg representing fatal illness.

cases in which a virus was detected were asymptomatic (Byington et al., 2015).

Asymptomatic cases are also commonly associated with COVID-19 but since most studies are conducted on ill patients referred to hospital the asymptomatic and mild illness in the community due to SARS-CoV-2 infection is not well reported. An analysis of SARS-CoV-2 infections looking at over 350 studies tried to determine the incidence of cases that were truly asymptomatic and found that over a third of infections fell in this category (Sah et al., 2021). Another analysis looking at 14 studies on COVID-19 estimated that up to 75% of cases were asymptomatic (Moradi et al., 2021). These studies indicate that although COVID-19 may be associated with severe lower respiratory tract symptoms the disease is similar to that caused by other respiratory viruses, and asymptomatic or very mild illness is a common result of SARS-CoV-2 infection especially for Omicron variant and subvariants (Sigal, 2022).

The symptoms caused by a respiratory virus infection are not specific to the virus and therefore it is not possible to identify the virus from any grouping of symptoms in a specific individual. A study on nasal challenge with three strains of rhinovirus, a coronavirus and a respiratory syncytial virus reported that “Patterns of symptom development were not substantially different with different viruses” (Tyrrell et al., 1993). Similarly, influenza viruses are commonly associated with flu-like illness, but a common result of infection is asymptomatic or mild illness like a common cold (Ip et al., 2017; Benet et al., 2021). Colloquially, “the flu” is often thought of as a more severe illness involving fever and prostration in addition to upper respiratory symptoms, but in fact influenza virus infections are often associated with afebrile illness more like the “common cold”, whereas other respiratory virus infections can sometimes produce febrile “flu-like” illness (Eccles, 2005).

Innate immune response for respiratory tract viral infections

The symptoms of URTI are predominantly caused by the innate immune response to the viral infection and can be divided into two components, as illustrated in Fig. 2. Systemic symptoms of fever, muscle aches and pains, headache and depressed mood are caused by cytokines (including IL-1, IL-6, IL-8, and RANTES among others) released from leukocytes and epithelial cells when pattern recognition receptors on these cells detect the presence of viral nucleotides and viral proteins (Eccles, 2005; Eccles, 2007; Kimura et al., 2013). COVID-19 is associated with a similar cytokine response to other respiratory viruses notably, increased levels of IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, IFN gamma, macrophage inflammatory protein 1 alpha (MIP1 alpha), and tumor necrosis factor (TNF)

Table 1
Respiratory viruses.

Virus	Abbreviation	Nucleic Acid	Classification	Structure
Rhinovirus	HRV	RNA	Species A,B, C with 100 serotypes	Non-enveloped icosahedral capsid
Coronavirus Seasonal	HCoV	RNA	Types OC43, 229E, NL63, HKU1	enveloped
Coronavirus Pandemic	SARS, MERS SARS-CoV2	RNA	Variants such as Omicron	enveloped
Respiratory syncytial virus	HRSV	RNA	Groups A and B	enveloped
Parainfluenza virus	HPIV	RNA	Types 1, 2, 3, 4	enveloped
Influenza virus	Flu	RNA	Types A,B,C,D	enveloped
Adenovirus	ADV	DNA	51 serotypes	Non-enveloped icosahedral capsid
Metapneumovirus	HMPV	RNA	Groups A and B	enveloped
Bocavirus	HBov	DNA	2 lineages	Non-enveloped icosahedral capsid

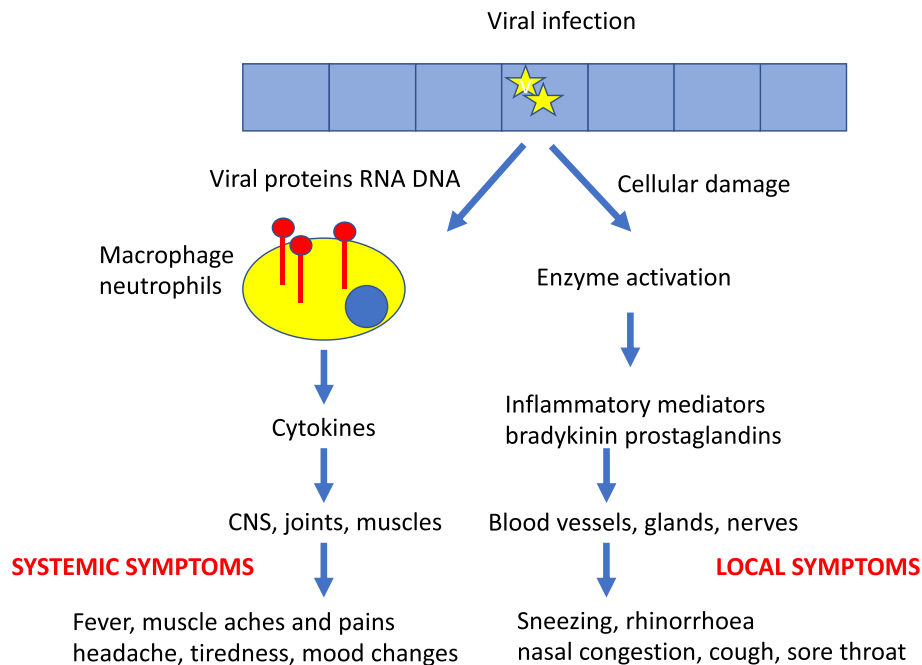


Fig. 2. Viral infection causes symptoms by two pathways. Local symptoms in the respiratory epithelium are caused by the generation of inflammatory mediators such as bradykinin and prostaglandins. Systemic symptoms are caused by cytokine release from leukocytes and epithelial cells when viral proteins and nucleotides are detected.

(Bohn et al., 2020). The individual cytokines released on infection with respiratory viruses have a great overlap in the symptoms they generate, as they are pleiotropic and redundant in that the same biological function can be executed by several distinct cytokines, and they have the ability to interact not with one but a variety of cellular targets, and the cytokine induced symptoms are similar for all respiratory viruses with a flu-like illness (Descotes et al., 2007; Whiteside et al., 2007).

Local symptoms of sneezing, rhinorrhoea, nasal congestion and sore throat are caused by a local inflammatory response in the upper airways caused by the formation of bradykinin and prostaglandins (Eccles, 2005; Eccles, 2007; Kimura et al., 2013). This review concerns the symptomatic treatments for common cold and flu-like illness.

The generation of symptoms as illustrated in Fig. 2 can be applied to all respiratory viruses as the innate immune response is non-specific (Mueller and Rouse, 2008) as demonstrated in cell culture and in patient samples (Ip et al., 2017). The range and severity of symptoms caused by respiratory virus infection will depend on several factors such as the age and immune status of the host. Infants commonly exhibit fever when infected with a respiratory virus whereas fever is much less common in the adult (Eccles, 2005). RSV infection in infants may result in bronchiolitis whereas older children and younger adults may develop only cold symptoms (Boncristiani et al., 2009), while RSV-related pneumonia does cause a substantial number of hospitalizations in older adults (Tin Tin Htar et al., 2020). Although COVID-19 has been recognised as a serious and separate disease from disease caused by other respiratory viruses, the generation of symptoms by SARS-CoV-2 infection has the same mechanisms of innate immune response as any other respiratory virus as illustrated in Fig. 2. As stated above, it is the innate immune response to viral infection that causes symptoms, and this response is not specific to any virus. The specific mechanisms and symptomatic treatments relating to common cold and flu-like symptoms will now be discussed and these have been previously reviewed by Eccles (Eccles, 2005; Eccles, 2007; Eccles and Kenakin, 2022) (Eccles, 2005; Eccles, 2007; Eccles and Kenakin, 2022).

Symptomatic treatments for symptoms associated with URTI

The signs and symptoms of URTI are not specific for any respiratory virus as they are generated by a non-specific innate immune response as discussed above. The mechanism of a symptom of URTI such as nasal congestion is the same for all respiratory viruses including COVID-19. Therefore, pharmacological interventions which treat a symptom are likely to be effective treatments for that symptom across all the respiratory viruses including SARS-CoV-2, as they influence the mechanism of the symptom and not the virus. The symptoms of URTI can be relieved by treatment with widely available medicines often referred to as over the counter (OTC) medicines. The consumer with URTI who purchases and uses a medicine does so in order to treat a symptom, and they do not routinely identify the virus causing the URTI. The consumer may identify the URTI as a common cold or flu, but prior to the COVID-19 pandemic there were no freely available at home tests to identify any respiratory virus causing the symptom. As discussed above, COVID-19 commonly presents as a mild common cold or flu-like illness and without any tests to identify the virus, the syndrome of mild symptoms with COVID-19 is similar to that of any other respiratory virus. At present OTC medicines are only licensed by regulatory authorities for the treatment of common cold and flu-like symptoms and they are not licensed for treatment of COVID-19 symptoms even though the COVID-19 symptoms may be the same common cold and flu like symptoms e.g. runny nose, sneezing, sore throat headache, muscle aches and pains, and fever.

All respiratory viruses can cause common cold and flu-like illness by the same mechanism of innate immune response and therefore it is reasonable that OTC medicines for the treatment of common cold and flu like illness be licensed by regulatory authorities for the treatment of these symptoms regardless of the causative virus.

Symptomatic treatment of COVID-19

The latest information from the World Health Organisation (WHO) on COVID-19 states that “Most infected people will develop mild to moderate illness and recover without hospitalization. People with mild symptoms

who are otherwise healthy should manage their symptoms at home” (WHO, 2022). Those with mild symptoms who are managing their symptoms at home will turn to readily available OTC medicines to alleviate the severity of symptoms. The sale of OTC medicines greatly increased during the COVID-19 pandemic and a study from Sweden reported that there was a 96% increase in sales over some periods of the pandemic compared to previous years (Karlsson et al., 2021). The WHO lists fever, cough, sore throat, headache and muscle aches and pains as symptoms associated with COVID-19 (WHO, 2022). In a study based in London UK in 2021 with data from 52,489 positive swab tests the top five most common symptoms reported for COVID-19 by the general public were runny nose, headache, fatigue, sneezing and sore throat (Lacobucci, 2021). Some of the most commonly used OTC treatments for relief of common cold symptoms are listed in Table 2. All of the medicines listed in Table 2 are accepted as safe and effective treatments (when used as directed) for common cold and flu-like symptoms by regulatory authorities such as the Food and Drug Administration (FDA) in the United States, Medicines and Healthcare products Agency (MHRA) in the United Kingdom, Therapeutic Goods Administration (TGA) in Australia and the European Medicines Agency (EMA) in the European Union. These medicines have been used as symptomatic treatments for cold and flu for decades, for example the FDA approved dextromethorphan for use as a safe and effective cough suppressant in 1958 (Oh, 2022). It is not the purpose of this review to detail the safety and efficacy of all the OTC medicines used to treat cold and flu-like symptoms and the safety and efficacy of these medicines has been recently reviewed (Eccles and Kenakin, 2022). The issue of concern in this review is if these OTC treatments are safe and effective for treatment of common cold and flu-like illness associated with COVID-19. To date there have been no clinical trials to establish the safety and efficacy of the medicines listed in Table 2 for the treatment of COVID-19 symptoms. However, these medicines act downstream of the innate immune response on blood vessels, nerves and glands that are responsible for the symptoms listed in Table 2 (Eccles, 2005). The mechanism of these symptoms are the same for all respiratory viruses as discussed above. Therefore, it can be assumed that OTC medicines will be effective to treat common cold and flu-like symptoms associated with all respiratory viruses including SARS-CoV-2.

Safety of OTC medicines for treatment of symptoms of COVID-19

As a novel respiratory virus infecting man SARS-CoV-2 and its disease state COVID-19 has been dealt with as a novel disease separate from the common cold and flu-like illnesses caused by all other respiratory viruses. The recommendation from the WHO that the disease can now be managed at home indicates that COVID-19 is being treated in the same way as all other respiratory viruses when it causes mild symptoms. However, there has been some speculation that OTC treatments such as

Table 2
Treatments for common cold and flu-like symptoms.

Symptom	Treatment Class	Medicines
Fever	Analgesic antipyretic	paracetamol (acetaminophen), aspirin, ibuprofen
Headache	Analgesic antipyretic	As above
Muscle aches and pains	Analgesic antipyretic	As above
Sore throat pain	Analgesic antipyretic	As above
Sinus pain	Analgesic antipyretic	As above
Nasal congestion	Sympathomimetics	oxymetazoline, xylometazoline, phenylephrine, pseudoephedrine
Runny nose	Anticholinergics and sedating antihistamines	ipratropium, and antihistamines as below
Sneezing	Sedating antihistamines	diphenhydramine, chlorpheniramine
Cough	Antitussives	dextromethorphan

ibuprofen used to treat fever may worsen the outcome of COVID-19 (Jamerson and Haryadi, 2020). These concerns were put forward as a hypothesis that treating fever with antipyretics could reduce any beneficial effects of fever in overcoming the infection. The role of fever and the use of antipyretics has been debated since the first antipyretic aspirin was invented over a hundred years ago, and recent reviews on this issue still do not provide any clear answer to the question “should fever be treated with antipyretics” (Harden et al., 2015). The hypothesis that treating fever with ibuprofen may worsen the outcome of COVID-19 (Jamerson and Haryadi, 2020) has not been supported by any clinical data and more recent studies indicate that treatment with ibuprofen may improve the outcome by suppressing the inflammatory response (Pandeloni et al., 2022). The analgesic antipyretics ibuprofen, paracetamol and aspirin have a similar mechanism of action as they all inhibit the activity of cyclooxygenase (COX) enzymes which are involved in the synthesis of prostaglandins and related inflammatory mediators (Eccles et al., 2003; Ferreira, 1986; Kantor, 1993). The pain symptoms of URTI such as sore throat pain, sinus pain, headache, and muscle aches and pains are relieved by these analgesics as pain in all these cases involves the generation of prostaglandins which sensitize pain nerve endings to the effects of bradykinin (Eccles, 2005). It is reasonable to assume that since these analgesic antipyretics are safe and effective in treating symptoms of URTI they will be safe and effective in controlling the same symptoms associated with COVID-19.

Similar to the analgesic antipyretics, there is no evidence from clinical trials that the other classes of OTC medicines listed in Table 2, sympathomimetics, anticholinergics, antihistamines and antitussives, are safe and effective in treating symptoms associated with COVID-19. However, if it is accepted that the mechanisms of symptoms for URTI and COVID-19 are the same one can assume efficacy for symptomatic treatment of COVID-19. There is no evidence in the literature for any specific safety issues relating to treatment of COVID-19 symptoms with OTC medicines. As with all medicines, overdose and misuse of OTC medicines may be associated with toxicity but this has not been found in any of the published literature on COVID-19 to date. The safety of OTC medicines is under constant review, and rare interactions with other medicines is sometimes discovered, as with the interaction of the antitussive pholcodine with neuromuscular blocking agents used in general anaesthesia, which has caused the withdrawal of pholcodine from sale (Mertes et al., 2023; Mahase, 2023).

Discussion

The COVID-19 pandemic has resulted in the deaths of over 6 million persons (WHO, 2022). However, with increased exposure of the world population to SARS-CoV-2 virus and mass vaccination programmes this serious disease, in the majority of the population, is now considered to have evolved into a much milder disease resembling a common cold or flu-like illness that can be treated at home. OTC treatment of mild cases of COVID19 at home would alleviate burden on hospitals during high incidence of COVID-19 in the population. As discussed above, the mechanisms of the symptoms of URTI are the same for all respiratory viruses including SARS-CoV-2 and these symptoms can be relieved by treatment with a range of OTC medicines. This review provides scientific information that OTC treatments for common cold and flu-like illness caused by respiratory viruses are safe and effective treatments for the same symptoms associated with COVID-19.

Conclusions

OTC treatments for the symptoms of common cold and flu-like illness are also safe and effective treatments for these symptoms when associated with COVID-19.

Ethical approval statement

No ethical approval was required for this review article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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