Role of
N-Acetylcysteine
in the treatment of
Acute
Respiratory
Disorders
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1. Introduction

The use of N-acetylcysteine (NAC) as an oral mucolytic in the treatment of respiratory disorders has become an accepted and widespread treatment option in many countries worldwide. The focus of this review is the use of oral NAC in treating acute respiratory pathologies:

- productive (wet) cough
- acute bronchitis
- influenza.

The mechanisms of action of NAC in these indications include mucolytic, anti-inflammatory, antioxidant and immunomodulatory effects. NAC is recommended for the treatment of acute respiratory conditions in a range of patients including adults and children (figure 1).

NAC was first developed and used as a mucolytic in respiratory diseases, but subsequent research revealed its antioxidant properties. NAC is therefore also effective in reducing oxidative stress and inflammation in the airways and lungs, produced by cigarette smoke or airborne pollution. Recently, NAC has also been shown to stimulate activation of the immune system.

In addition to its use in the treatment of acute respiratory conditions, NAC is used as part of the standard regimen in the management of chronic obstructive respiratory disease, in the management of acetaminophen (paracetamol) poisoning and in other indications however, a discussion of these indications is beyond the scope of this monograph.

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**Fig. 1**
Acute respiratory conditions for which pharmacists can advise using N-acetylcysteine (NAC).

- Patient presents with acute respiratory condition
- Acute bronchitis
- Influenza
- Productive (wet) cough, catarrh
- NAC
  - Recommend treatment with oral NAC (tablets, granules or ready-to-use-syrup)
- Adults and children aged > 12 years: 600 mg/day
- Children aged < 12 years: 300-600 mg/day
2. Mucociliary System

The mucociliary system has many functions including:

- hydrating airways
- uptaking and transporting inhaled particles to the pharynx
- biologically purifying against bacterial invasion
- maintaining bronchial tone.

Mucociliary transport is an important defense mechanism in the human body; it moves airway mucous, together with any trapped substances (e.g. inhaled particles or endogenous debris), out of the lungs. When necessary, cough also helps to remove excessive airway secretions. The fluidity of mucous is reduced by the formation of disulfide bridges; this, in turn, impairs the efficiency of mucociliary clearance and increases the difficulty of expectoration (figure 2).

In many acute respiratory conditions there is an excessive secretion of mucous. In addition, patients who smoke cigarettes have an increase in tissues that secrete mucous, increases in mucous production, and increased mucous viscosity. Reducing excessive or thick mucous and improving mucociliary transport is important as mucous retention may lead to bacterial colonization, which may result in pneumonia. In influenza viral infections, rapid movement of the mucous is useful in trapping and physically removing the virus before it can penetrate the blanket of mucous. As involuntary cough affects quality of sleep, improving mucous clearance will also help reduce coughing and improve the health-related quality of life of the patient.

![Fig. 2](image-url)
3. Inflammatory Process

Many mechanisms are involved in the inflammatory process including mediators, gene expression, oxidative stress and free radicals.[7,10-12] Oxidative stress, an important part of the inflammatory response to both environmental and internal signals, results from the production of oxygen-free radicals and other oxidant agents. Endogenous and exogenous oxidants (any molecule with an unpaired electron on its outer orbit) are capable of injuring the lung.[10,13] Free radicals are highly reactive molecules that can either donate (reduce) or abstract (oxidize) an electron to other nearby molecules. These reactive species also activate transcription factors, leading to the release of proinflammatory cytokines and thus an increase in the inflammatory response.[7,14] Therefore, it appears that oxidative stress and inflammation are inseparable phenomena (figure 3).

Oxidative stress is responsible for alterations in many components of the lungs, including the airway wall, alveolar epithelial cell layer, lung matrix, pulmonary microcirculation and transcription factors.[14] Oxidative stress causes an amplified inflammatory response, lipid peroxidation and cell membrane damage, which results in acute inflammation, increased mucous secretion and tissue damage (figure 3). In turn, each of these results in clinical effects, such as difficult expectoration and risk of infection, cough, bronchoconstriction, and decline in lung function. In addition to initiating inflammation, cell and tissue injury caused by oxidative stress maintains inflammation.[12]

Antioxidants neutralize free radicals and restore the reductive-oxidative (redox) balance and, therefore, reduce the damage to cells and DNA caused by free radicals.[10,13]

3.1 Role of Cigarette Smoke and Air Pollution

Oxidants are produced by cells in the human body, but cigarette smoke and atmospheric pollution are also a source (figure 4).[7,10,13,15,16] Free radicals and potent catalysts of oxidation reactions (e.g. iron and other...
transition metals) are present in large amounts in cigarette smoke, leading to oxidative stress and airway inflammation. Smokers have greater levels of some systemic inflammatory markers than nonsmokers. Air-borne pollutants (e.g. from fossil fuel combustion products, diesel exhaust particles and residual oil fly ash) contribute to respiratory illness in urban and industrial areas. Particulate air pollution has proinflammatory activities (e.g. release of inflammatory markers and generation of free radicals) similar to those seen with cigarette smoke. The lung can be protected by:

- reducing the oxidant burden (e.g. limiting exposure to cigarette smoke or air-borne pollutants)
- increasing antioxidant defenses by increasing normal antioxidants (e.g. enzymes [superoxide dismutases, catalase, glutathione peroxidase] and vitamins E and C) or by administering exogenous antioxidants, such as NAC, that have well established antioxidant properties.

Fig. 4
Role of cigarette smoke and atmospheric pollution on oxidative stress and inflammation in airways and lungs.
The pathogenesis of influenza and other viral infections and the age-related deterioration of the immunomodulatory system are related, in part, to:

- redox imbalance
- oxidative stress
- increases in inflammatory mediators.

The epithelial cell layer of the respiratory tract undergoes pathological change during influenza virus infection. When respiratory cells are infected with pathogenic viruses, oxidant production in respiratory cells increases. At the same time, stores of naturally occurring antioxidants, in particular glutathione, are depleted. Oxidants are involved in the activation of transcription factors for inflammatory protein genes and the development of pulmonary cell damage. Moreover, oxidative stress alters the local immune response, increasing the risk of infection. Therefore, antioxidants have a role in the treatment of viral infections: they defend against viral-induced oxidation by reactive species and also prevent the release of inflammatory mediators. This improves immune function and prevents pulmonary cell damage under conditions of oxidative stress. A redox imbalance, which leads to oxidative stress resulting in a deterioration of the function of immune cells (e.g. neutrophil and lymphocyte activity) occurs with aging. Antioxidant treatment may, therefore, restore the function of some immune systems in older patients by directly affecting the immune system or indirectly as a result of its antioxidant properties.
5. N-Acetylcysteine

5.1 Historical Use
NAC has been used in clinical practice since the 1960s.[1] A 5% to 10% NAC solution administered by aerosol or instillation into the bronchopulmonary tree was shown to be an effective mucolytic in various respiratory diseases. Since the 1970s, pleasant-tasting oral NAC preparations have been available in many countries of the world. The oral formulations are effective in treating respiratory disorders with thick and productive cough, and are well accepted by patients.

5.2 Chemical Structure
NAC is a precursor of both the naturally occurring simple amino acid cysteine and reduced glutathione.[24] Due to the presence of the acetyl substituted amino group, NAC is less easily oxidized to inactive cystine than cysteine.[1] NAC is a thiol (sulfhydryl)-providing compound; the thiol group ruptures disulfide bridges in mucoproteins and is responsible for its mucolytic activity (section 6).[1]

5.3 Pharmacokinetic Profile
Tables I and II provide a brief summary of the pharmacokinetic properties of orally administered NAC.[25] The pharmacokinetics of oral NAC appear to be dose proportional, and NAC does not accumulate in the plasma after repeated dosing.[26] Following oral administration, NAC is quickly and completely absorbed from the gastrointestinal tract. It undergoes rapid, extensive metabolism in the gut wall and liver.[27] The active NAC metabolites (cysteine and reduced glutathione), and not NAC itself, are likely to be responsible for most of the observed pharmacological and clinical effects. The plasma concentration of free cysteine increases significantly after administration of NAC. The elimination half-life of free cysteine in the plasma is ≈0.81 hours.

NAC may be present in plasma and tissues as:[27]
- the parent compound or active (cysteine and reduced glutathione) or inactive metabolites
- a releasable fraction bound to proteins by disulfide linkages
- a fraction incorporated into protein chains.

Table I  Summary of the pharmacokinetic properties of oral N-acetylcysteine (NAC)[25]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption Characteristics</td>
<td>Rapid and complete</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>Found in body as free NAC and reversibly bound to plasma proteins through disulfide links</td>
</tr>
<tr>
<td>Bioavailability of free NAC after hepatic first passage</td>
<td>≈10%</td>
</tr>
<tr>
<td>Distribution</td>
<td>Aqueous environment of the extracellular space</td>
</tr>
<tr>
<td>Primary spread</td>
<td>Liver, kidneys, lungs and bronchial mucous</td>
</tr>
<tr>
<td>Initial</td>
<td>Rapidly deacetylated in the intestinal wall and through hepatic first passage to active L-cysteine</td>
</tr>
<tr>
<td>Secondary</td>
<td>Metabolized to inactive forms</td>
</tr>
<tr>
<td>Clearance</td>
<td>≈30%</td>
</tr>
<tr>
<td>Renal</td>
<td>Cystine and cysteine</td>
</tr>
</tbody>
</table>

Table II  Summary of the pharmacokinetic properties of N-acetylcysteine (NAC) 30mg/kg[25]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Free and bound NAC</th>
<th>Free NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (nmol/mL)</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>Time to Cmax (h)</td>
<td>0.75–1</td>
<td></td>
</tr>
<tr>
<td>Area under the curve (nmol/mL × h)</td>
<td>163</td>
<td>12</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>1.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Cmax = peak plasma concentration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Mucolytic Activity

NAC has two primary mechanisms of action as a mucolytic (figure 5):[24]

- direct mucolytic activity. The thiol groups in NAC rupture the disulfide bridges of proteins in the mucous, resulting in smaller units of the protein and, therefore, reduced viscosity and mucous that is easier to expectorate
- activation of mucociliary clearance. The physiological transport of mucous and, therefore, its removal is improved by NAC.

The favourable effects of NAC as a mucolytic have been shown in numerous in vitro and animal-model studies and studies in patients (table III) [28-40] NAC reduced the viscosity of mucous, improved its transport and increased sputum volume.

NAC also had a beneficial effect on mucous induced by cigarette smoke (table III). It improved mucociliary action,[28] decreased the length of time necessary to reverse mucous cell hyperplasia[29] and inhibited hypersecretion of mucous in the larynx and trachea.[30]

6.1 Clinical Trials

The efficacy of NAC as a mucolytic in patients with respiratory conditions, such as chronic obstructive pulmonary disease (COPD) or chronic bronchitis, is well established.[7,24,41] Oral NAC has favorable effects on mucous and cough in patients, including children, with acute or chronic respiratory disorders.

The focus of this monograph is the relatively short-term (10–15 days) use of oral NAC in the treatment of acute respiratory conditions.[42,44] In these trials, the efficacy of treatment was assessed using the differences between baseline and endpoint values in various clinical parameters.[42-44] Sputum viscosity, cough severity, difficulty of expectoration and dyspnea were each scored on a 3- or 4-point scale, where the lowest scores of 0 or 1 indicate ‘normal’ function (e.g. absence of cough) or few symptoms (e.g. very fluid sputum) and 3 points indicates highly pathological conditions (e.g. very viscous sputum or intense cough during the day or night).

NAC reduces the viscosity of expectorations, which reduces the expectoration difficulties and the severity of productive cough. In the short-term clinical trials, oral NAC 200mg three times daily used alone or concomitantly with antibiotics (amoxicillin 1.5[42] or 2 g/day[43,44]), decreased the consistency of sputum, facilitated its expectoration and reduced cough and thoracic physical symptoms.[42-44] NAC was more effective than placebo in the largest of the short-term trials.[42] In this trial in 215 patients with acute bronchitis, superinfections of chronic bronchitis, or complicated bronchitis in patients with severe chronic respiratory insufficiency, patients received NAC 200mg three times daily for 10 days. Compared with baseline, patients receiving NAC showed significant improvements in all parameters (sputum expectoration, sputum viscosity, cough and peak expiratory flow rate [PEFR]). Moreover, NAC was significantly more effective than placebo in decreasing sputum viscosity.

### Table III  Summary of mucolytic effects of N-acetylcysteine in in vitro studies, animal models and studies in patients with excess respiratory mucous

| In vitro | Reduced viscosity of mucous[31-34] |
| Direct and immediate effect on decreasing the viscoelastic properties of bronchial secretions[35] |
| Inhibited Na+ absorption across human nasal epithelial cells, which may increase mucous fluidity[36] |
| Reduced the deleterious effect of cigarette smoke extract on mucociliary action[37] |

| Animal models | Increased mucous velocity and ciliary beat frequency[37] |
| Increased the volume of respiratory tract fluid and decreased viscosity of sputum[38] |
| Reduced the time required to reverse smoke-induced mucous cell hyperplasia[39] |
| Inhibited cigarette smoke-induced hypersecretion of mucous in larynx and trachea[39] |

| Studies in patients | More effective than saline in reducing sputum viscosity and consistency and increasing sputum volume in patients with chronic bronchial disease[2,39] |
| Improved mucociliary transport in heavy smokers with hypersecretory bronchitis and reduction in mucociliary transport[40] |
increasing sputum expectoration, preventing cough and increasing PEFR (all \( p < 0.0001 \)). The greatest efficacy was shown in patients with acute or chronic bronchitis. Figure 6 shows the improvements from baseline in clinical parameters with NAC compared with placebo in patients with acute bronchitis. The increase in the volume of sputum shown in the group receiving NAC was probably due to the
Table IV Efficacy of oral N-acetylcysteine (NAC) in the treatment of acute respiratory diseases in children in selected clinical trials

<table>
<thead>
<tr>
<th>Study (no. of children)</th>
<th>Acute respiratory condition</th>
<th>Treatment regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biscatti et al.[47] (50)</td>
<td>Acute respiratory tract infections</td>
<td>Oral NAC 100–300mg/day (according to age) or placebo for 6 days All patients received the most suitable antibacterial agent</td>
<td>Fever, cough, dyspnea and thoracic moist rates returned to normal in a significantly shorter time with NAC than with placebo</td>
</tr>
<tr>
<td>Hofman[48] (49)</td>
<td>Asthma, sinobronchial syndrome or severe, purulent bronchitis</td>
<td>Not stated</td>
<td>Subjective improvement in all patients Improved sinusitis when it was not chronic and purulent Improved most cases of bronchitis</td>
</tr>
<tr>
<td>Nikolić &amp; Korac[45] (20)</td>
<td>Bronchitis (afebrile acute recurrent bronchitis frequently accompanied by signs of bronchial allergy; febrile recurrent or catarrhal bronchitis; or simple catarrhal bronchitis)</td>
<td>Oral NAC 100 or 200mg three times daily (according to age) for 4 days Only patients with acute febrile bronchitis received antibacterials</td>
<td>Shortened the duration of catarhall inflammation of the throat and cough Returned vital capacity and pulmonary air flow values to normal in patients with simple or recurrent catarhall bronchitis after 4 days of treatment</td>
</tr>
<tr>
<td>Ribeiro et al.[46] (67)</td>
<td>Obstructive bronchial diseases (atelectasis, bronchiolopathy, pseudobronchiectasis, bronchiectasis, cystic fibrosis, lung abscess, chronic bronchitis, combined pathology)</td>
<td>NAC 10–50mg/kg/day in 2 or 3 divided doses for 7–110 days (mean 26 days) All patients had previously received other treatments without success or only partial success</td>
<td>Improvement shown in most patients The majority (&gt;80%) of patients had excellent-to-good clinical and radiological results (Fig. 8)</td>
</tr>
</tbody>
</table>

Fig. 7
Efficacy of oral N-acetylcysteine (NAC) in the treatment of patients with bronchitis. Mean changes from baseline at day 10 for various clinical parameters in patients receiving oral NAC 200mg three times daily, placebo or bromhexine 8mg three times daily in a 10-day trial.[59] *p < 0.05, **p ≤ 0.01, ***p < 0.001 vs baseline.
decrease in mucus viscosity, which facilitated drainage of bronchial secretions. NAC is more effective than bromhexine or placebo when used together with antibacterials, whereas bromhexine and placebo have similar efficacy. In a 10-day trial in 54 patients with acute infections complicating COPD or acute respiratory infections, oral NAC 200mg three times daily significantly improved most clinical parameters of mucous, cough and functional parameters from baseline (figure 7). Mean changes in baseline in several parameters (sputum viscosity, cough, difficulty of expectoration and forced expiratory volume in 1 second [FEV1]) were significantly greater with NAC than with placebo or bromhexine 8mg three times daily (all *p* < 0.05). In contrast, there were no significant differences between placebo and bromhexine in changes from baseline for any parameter. Changes in functional respiratory parameters are secondary to the clearing of the airways; the combination of NAC and an antibacterial cleared the airways better than antibacterials alone or combined with bromhexine, leading to improvements in FEV1 and forced vital capacity values (figure 7).

NAC was also more effective than bromhexine in a 15-day trial in 60 patients with non-infectious chronic bronchitis or acute respiratory infections. NAC reduced sputum thickness, difficulty in raising sputum, cough and dyspnea to a significantly greater extent than bromhexine (all *p* < 0.05). For example, compared with bromhexine, NAC reduced sputum viscosity more rapidly and effectively (*p* < 0.001). Moreover, NAC was more effective than bromhexine in treating patients in both of the treatment groups (i.e. when NAC was used concomitantly with antibacterial treatment in patients with acute respiratory infections and to an even greater degree in those with chronic non-infectious respiratory conditions).

### 6.1.1 Children

Oral NAC was also effective in treating children with acute respiratory conditions in clinical trials (table IV). Although it is difficult to evaluate objective parameters of mucolytic activity in children (e.g. they may not fully cooperate in spirographic testing or mucus collection), objective and/or subjective improvements in a variety of parameters were shown with treatment with oral NAC in children with a range of diseases of the respiratory system. For example, both clinical and radiological results were favourable with oral NAC in children with a variety of obstructive respiratory diseases (figure 8 and table IV). Oral NAC is, therefore, a useful option in the treatment of respiratory diseases in pediatric patients.
7. Anti-Inflammatory and Antioxidant Activity

The mechanism of action of NAC as an anti-inflammatory is complex and involves both antioxidant activity and re-establishment of redox equilibrium (figure 9).\[7,14\] Oxidants and free radical attack cause inflammatory damage (section 3); therefore, agents with antioxidant activity, such as NAC, will inhibit the inflammatory process. NAC not only acts directly as an antioxidant, but also has indirect antioxidant properties as it is a precursor to biosynthesis of the antioxidant glutathione (figure 10).\[7,14\] Pulmonary tissues have a variety of both intracellular and extracellular antioxidant defense systems in order to counterbalance the production of free radicals and cope with the normal oxidative burden within the lungs. Antioxidant defense systems include antioxidant molecules and enzymatic systems, the most important of which is glutathione and its related complex enzymatic systems.\[7,12,24\] Glutathione directly detoxifies reactive species by conjugation and/or reduction; the enzyme systems enhance chemical detoxification by catalyzing conjugation reactions and reductions.\[7,12,24\] Glutathione has also been implicated in numerous cellular functions.\[12,14\] Inflammation is mediated by inducible transcription factors that switch on the genes for inflammatory proteins. Reactive species activate this transcription, leading to the release of proinflammatory cytokines.\[7\] Therefore, to neutralize reactive species and prevent activation of transcription of inflammatory protein genes, the cellular redox equilibrium between reduced glutathione and its oxidized species glutathione disulfide must be maintained (figure 10).\[7,14\] It is essential to maintain adequate intracellular levels of glutathione to overcome the harmful effects of reactive species. Depletion of glutathione is caused by its antioxidant activity and also by elimination of oxidized glutathione from the cells. Once oxidized glutathione is eliminated from the cell, it is not available to be regenerated to reduced glutathione via the reductase pathway. The rate-limiting substrate in the synthesis of glutathione is cysteine.\[7,12,24\] Cysteine is difficult to administer as it is poorly absorbed, has low solubility in

![Fig. 9](image-url)
water and undergoes rapid hepatic metabolism. However, additional cysteine may be delivered by the administration of NAC because it is a precursor to cysteine. NAC increases the endogenous supply of cysteine, either by deacetylation of NAC or through reduction by NAC of endogenous cystine into cysteine. Relative to cysteine, NAC is well absorbed intestinally, has good water solubility, is stable to oxidation and is well tolerated.

Administration of NAC results in increased levels of endogenous cysteine that:

• stimulate glutathione synthesis when there is an increased demand
• enhance the activity of enzymes dependent on glutathione
• promote antioxidant activity.

NAC, therefore, maintains the redox-equilibrium between reduced glutathione and oxidized glutathione and acts directly as an antioxidant, which leads to complete airway protection against oxidative stress and inflammation.

NAC inhibits the activation of some redox-sensitive signal transduction factors. Therefore, NAC prevents the release of proinflammatory cytokines and, as a result, would have longer-term effects on the inflammatory response than agents that inhibit only the inflammation mediators involved in the last steps of the inflammatory process.

The anti-inflammatory and antioxidative actions of NAC have been shown in many in vitro and animal-model studies. 

7.1 Patients with chronic obstructive pulmonary disease

The anti-inflammatory and antioxidative actions of NAC have also been demonstrated in studies in patients with COPD. Markers of oxidative stress and inflammation were reduced in the red blood cells, sputum and blood of these patients. Oral NAC decreased levels of C-reactive protein, which is a marker of inflammation, in patients with acute exacerbations of COPD. This double-blind 10-day study compared the efficacy of two dosage regimens of oral NAC (600 or 1200mg/day) with that of placebo in reducing the levels of C-reactive protein and other indicators of inflammation in 122 patients with an acute exacerbation of COPD.

Levels of C-reactive protein decreased to a greater extent with NAC than with placebo at day 5 and day 10 of the trial. The improvement was greater with the
Table V  Summary of the protective function of N-acetylcysteine against cigarette smoke or air-borne pollution in in vitro studies, animal models and studies in cigarette smokers

**In vitro**
Protected against oxidant-mediated cytotoxicity induced by cigarette smoke[^49]
Decreased toxicity due to tobacco smoke[^50]
Improved the survival of cultured human bronchial cells exposed to tobacco smoke condensate[^51]
Protected against the loss of pulmonary glutathione and cell toxicity associated with cigarette smoke[^51]
Glutathione and cysteine protected macrophage cells from the effects of tobacco smoke[^52]
Reduced stimuli-induced superoxide radical generation by human alveolar macrophages from smokers[^53]

**Animal models**
Attenuated secretory cell hyperplasia induced by tobacco smoke[^54]
Protected against acetaldehyde lethality; more effective on an equivalent mole basis than L-cysteine or L-ascorbic acid[^55]
Protected against chloroacetaldehyde and metabolically formed acrolein[^56]
Prevented thickening of the airway wall and improved distribution of ventilation in a model of cigarette smoke-induced alterations to small airways[^56]
Prevented lung inflammation after short-term exposure to inhaled concentrated ambient particles[^57]
Increased levels of interferon-γ and normalized interferon-γ : interleukin-4 ratios[^58]

**Studies in healthy smokers**
Reduced the levels of some markers of inflammation[^59]
Reduced the stimulated production of free oxygen radicals[^52]
Exhibited defensive mechanism against aggressive agents[^60]

---

**Fig. 11**
Effect of oral N-acetylcysteine (NAC) 600 or 1200 mg/day on levels of a marker of inflammation (C-reactive protein; CRP). Levels of CRP at baseline and at day 5 and day 10 of treatment and the proportion of patients that achieved normal CRP levels at day 10 in patients with an acute exacerbation of chronic obstructive pulmonary disease.[^89]

* p < 0.001 vs baseline; † p < 0.001 vs placebo; ‡ p = 0.002 vs NAC 600mg/day.
NAC is useful in respiratory conditions caused by oxidative stress and inflammation in the airways that are induced by cigarette smoke and air-borne pollution (section 3.1).[7] When excessive amounts of oxidants are inhaled from cigarette smoking or air-borne pollution, the normal oxidant burden in the lungs is increased and oxidative stress may occur, resulting in lung injury.[16]

In addition to its beneficial effects as a mucolytic (section 6), NAC has antioxidant properties and the ability to maintain the glutathione redox equilibrium (figure 9). Acting as a direct antioxidant and a precursor of glutathione synthesis, NAC has a beneficial effect by increasing the antioxidant levels and neutralizing the increased oxidant burden.

Table VI  Summary of antioxidant and anti-inflammatory effects of N-acetylcysteine in in vitro studies and animal models

<table>
<thead>
<tr>
<th>In vitro</th>
<th>Animal models</th>
<th>Studies in patients with chronic obstructive pulmonary disease (COPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supported intracellular glutathione synthesis[16,61]</td>
<td>Reduced pulmonary response to endotoxin in a model of adult respiratory disease syndrome[85]</td>
<td>Reduced markers of oxidative stress in red blood cells in patients[96]</td>
</tr>
<tr>
<td>Acted as a scavenger of reactive species[16,61]</td>
<td>Prevented the release of granulocyte aggregates following endotoxin-induced lung injury[96]</td>
<td>Decreased markers of inflammation in sputum and blood in patients with stable COPD[97]</td>
</tr>
<tr>
<td>Decreased oxidant-mediated cytotoxicity[95,96]</td>
<td>Improved immune function in a model of premature ageing[92]</td>
<td>Decreased levels of activated protein C, a marker of inflammation, in patients with acute exacerbations of COPD[98]</td>
</tr>
<tr>
<td>Inhibited activation of a mitogen-activated protein kinases resulting in reduced release of chemokines[82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protected cells against death induced by exposure to noxious stimuli[82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protected against programmed cell death (apoptosis) associated with exposure to inadequate amounts of trophic factors[80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered lung oxidant : antioxidant imbalance[74]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other parameters of disease severity (including the frequency and severity of severe cough and difficulty in expectoration) also improved with treatment with NAC.[69] In contrast, the group receiving placebo did not show significant improvement from baseline in these parameters.

7.2 Protection from the Effects of Cigarette Smoke or Air-borne Pollution

NAC is useful in respiratory conditions caused by oxidative stress and inflammation in the airways that are induced by cigarette smoke and air-borne pollution (section 3.1). When excessive amounts of oxidants are inhaled from cigarette smoking or air-borne pollution, the normal oxidant burden in the lungs is increased and oxidative stress may occur, resulting in lung injury.[16]

In addition to its beneficial effects as a mucolytic (section 6), NAC has antioxidant properties and the ability to maintain the glutathione redox equilibrium (figure 9). Acting as a direct antioxidant and a precursor of glutathione synthesis, NAC has a beneficial effect by increasing the antioxidant levels and neutralizing the increased oxidant burden.

1200mg/day regimen than with the 600mg/day regimen. The proportion of patients that achieved normal C-reactive protein levels was significantly greater with NAC 1200 mg/day than with NAC 600mg/day or placebo (figure 11). NAC 1200mg/day also reduced interleukin-8 levels, another marker of inflammation, to a significantly greater extent than NAC 600mg/day or placebo (both p = 0.01).[95] Other parameters of disease severity (including the frequency and severity of severe cough and difficulty in expectoration) also improved with treatment with NAC.[69] In contrast, the group receiving placebo did not show significant improvement from baseline in these parameters.

16
status in patients with pulmonary inflammation induced by cigarette smoke or air-borne pollution. Exposure to particulate matter induces transcription of many proinflammatory genes; therefore, the activity of NAC in maintaining cellular redox equilibrium will also play a role in its protective effects. The various mechanisms of action of NAC will result in the inhibition of the inflammatory process induced by cigarette smoke or air-borne pollution and improve the clearance of mucous (figure 12).

In *in vitro* and animal-model studies, the action of NAC as an antioxidant offered protection against cigarette smoke or air-borne pollution (*table V*). Oral NAC also had beneficial effects on markers of inflammation in healthy smokers (*table V*). In three studies in healthy smokers,[53,59] the effects of treatment with oral NAC 200mg three times daily on bronchoalveolar lavage fluid were assessed. NAC significantly reduced the levels of some markers of inflammation[59] and reduced the stimulated production of free oxygen radicals.[53] Following NAC treatment, there was an increase in lymphocyte concentrations, improvement in the phagocytic activity of alveolar macrophages and an increase in leukotriene B4 secretion.[60] These activities indicated that NAC has important defense mechanisms against toxic agents.
8. Immunomodulatory Activity

NAC has shown beneficial effects on the immune system in many in vitro studies and animal models (Table VII) and also in studies in patients. The antioxidant activity of NAC appears to play a role in its efficacy in improving immune function. The pathogenesis of influenza and other infections, and age-related decreases in immune function involve oxidative stress, redox imbalance and the production of inflammatory cytokines (section 4). NAC may also have a direct action on immune cells; it improves the local immune response by protecting the function of lymphocytes and macrophages when exposed to reactive oxygen species in vitro. In addition, it is the precursor to glutathione, which has been shown to play a pivotal role in regulating, directly or indirectly, antimicrobial activity in immune cells (particularly macrophages). In mice models of respiratory influenza, NAC increased the resistance to the virus and reduced influenza-associated mortality. Beneficial effects on immune function were also shown in patients at risk of influenza infection (section 8.1) and in postmenopausal women (section 8.2). Therefore, NAC can protect against viral infection by improving the defenses against the virus and by protecting against the development of inflammation in the lung.

Table VII Summary of the immunomodulatory activity of N-acetylcysteine in in vitro studies and animal models and studies in patients

<table>
<thead>
<tr>
<th>In vitro</th>
<th>Animal models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protected lymphocytes from the toxic activity of reactive oxygen species</td>
<td>Increased the resistance to influenza virus</td>
</tr>
<tr>
<td>Improved immune function of macrophages from mice with endotoxin-induced oxidative stress</td>
<td>Pretreatment reduced the virus-induced activation of oxidase-sensitive transcription factors</td>
</tr>
<tr>
<td>Improved immune function of lymphocytes from mice with endotoxin-induced oxidative stress</td>
<td>Pretreatment reduced the release of inflammatory cytokines</td>
</tr>
<tr>
<td>Reduced the mortality of mice intranasally infected with influenza virus</td>
<td>Reduced the mortality of mice infected with influenza virus</td>
</tr>
<tr>
<td>Increased the antiviral activity of ribavirin in a synergistic manner</td>
<td>Increased the antiviral activity of ribavirin in a synergistic manner</td>
</tr>
</tbody>
</table>

In mice models of respiratory influenza, NAC increased the resistance to the virus and reduced influenza-associated mortality. Beneficial effects on immune function were also shown in patients at risk of influenza infection (section 8.1) and in postmenopausal women (section 8.2). Therefore, NAC can protect against viral infection by improving the defenses against the virus and by protecting against the development of inflammation in the lung.
8.1 Clinical Trials

8.1.1 Effect on Influenza-like Symptoms

NAC reduced both the frequency and severity of influenza-like episodes in a randomized, double-blind trial (table VIII).\(^7\) Treatment with oral NAC 600mg twice daily for 6 months attenuated influenza-like symptomatology relative to placebo in patients without chronic respiratory diseases (the majority of the 190 evaluable patients were aged ≥ 65 years).\(^2\) The frequency of influenza-like symptoms was significantly less with NAC than with placebo (figure 14). When assessed on a monthly basis, significant between-group differences in the frequency of influenza-like episodes were shown during the period of greatest seasonal incidence of influenza in Europe (i.e. during the winter months of December to March [2–4 months after beginning treatment]). The severity of influenza-like symptoms was also less with NAC than with placebo.\(^2\) Of the 46 influenza-like episodes in the NAC-treatment group, 72% were classified as mild, 25% as moderate, and 2% as severe. In comparison, of the 99 episodes within the placebo group, 48%, 47%, and 6% were classified as mild, moderate, or severe, respectively.

The incidence of specific local influenza-like symptoms (coryza/rhinorrhea, sore throat, catarrh and cough) and general influenza-like symptoms (headache, myalgia) was significantly lower with NAC than with placebo (all p < 0.05).\(^7\) This indicates that NAC, in addition to its mucolytic effects, also has antioxidant and immunomodulatory activity.

Relative to placebo, NAC also significantly reduced the length of time spent in bed due to influenza-like symptoms.\(^2\) Indeed, 9 of the 10 patients with influenza-like symptoms who were not bedridden were receiving NAC. Conversely, of the 25 patients who were bedridden for ≥ 6 days, only 3 patients were in the NAC-treatment group.

The frequency of seroconversion towards influenza virus was similar in the NAC and placebo-treatment groups (29% vs 24%), indicating that NAC did not prevent subclinical infections. However, significantly fewer NAC recipients developed a symptomatic form of the condition (figure 15). This indicates that NAC had a protective effect with respect to clinically evident disease. In those patients who did not undergo seroconversion towards the virus (71% vs 76%), the proportion of patients experiencing an influenza-like episode was numerically, but not...
significantly, lower with NAC than with placebo (figure 15). Following NAC treatment, there was a progressive, significant shift from anergy to normergy in an evaluation of cell-mediated immunity. In general, anergy was defined as a lack of skin reactivity to any of the 7 tested antigens; hypoergic as skin reactivity to ≤ 2 of the 7 antigens; and normergy as skin reactivity to ≥ 3 antigens. As is common in elderly patients, a relatively high proportion of the patients in both of the treatment groups were anergic (~20%) or hypoergic (~48%) at the beginning of the trial. Throughout the study, there was significant increase from the baseline in the proportion of patients who were normergic in the NAC treatment group, but not in the placebo treatment group (figure 16). The change in the proportion of normergic patients was significantly greater with NAC than with placebo (p < 0.05).

These changes in cell-mediated immunity confirm the immunomodulatory properties of NAC. Patients who are elderly and/or have chronic pathological conditions are particularly vulnerable to viral respiratory diseases, as there is a general impairment in immune defenses, loss of antioxidants and reduced function of immunocompetent systems. Therefore, NAC may be of benefit in boosting the immune response in elderly and high-risk individuals during the influenza season.

Fig. 15  
Efficacy of oral N-acetylcysteine (NAC) 600mg twice daily compared with placebo in patients with or without seroconversion towards influenza virus. Proportion of patients experiencing influenza-like symptoms as related to seroconversion towards influenza virus. * p < 0.0001 vs placebo.

Fig. 16  
Effect of oral N-acetylcysteine (NAC) 600mg twice daily compared with placebo on cell-mediated immunity. Proportion of patients with cell-mediated normergy at baseline and after 6 months of treatment. * p < 0.001 vs baseline; † p < 0.05 vs placebo.
8.1.2 Effects on Aging-Related Changes in Immune Function

NAC improved age-related deterioration of immune function in a study in 36 postmenopausal women (18 aged 50–60 years and 18 aged > 70 years). The women, who were in overall good health, received oral NAC 600mg once daily for 2 months.

NAC significantly improved the immune function of neutrophils and lymphocytes (Table IX), indicating that there was a decrease in the oxidative stress of the cell and rejuvenation of immune function. Improvements from baseline were significant for all values in each of the age groups and in the combined treatment groups (Figure 17). Immune function of neutrophils and lymphocytes in the older women was restored to that of younger women. Improvements from baseline in age-depressed immune function in the group aged >70 years were generally greater than those in the group aged 50–60 years (Figure 17). At the beginning of treatment, baseline values for immune function parameters had deteriorated in the older age group compared with values in the younger age group, being significantly different in the case of lymphoproliferation in response to PHA and IL-2 liberation. The immune function values at the end of treatment in the older group were either significantly better or similar to baseline values in the younger group. This indicates that, in older people, NAC can restore some immune functions.

Table IX: Effects of oral N-acetylcysteine on the immune function of neutrophils and leukocytes in postmenopausal women.

<table>
<thead>
<tr>
<th>Effect on neutrophils</th>
<th>Effect on lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced adhesion</td>
<td>Reduced adhesion</td>
</tr>
<tr>
<td>Reduced superoxide levels</td>
<td>Reduced secretion of tumour necrosis factor-α</td>
</tr>
<tr>
<td>Stimulated mobility towards the infectious center</td>
<td>Stimulated mobility towards the infectious center</td>
</tr>
<tr>
<td>Stimulated phagocytosis of strange particles</td>
<td>Stimulated production of interleukin-2</td>
</tr>
<tr>
<td></td>
<td>Stimulated the proliferation response to phytohemagglutinin</td>
</tr>
<tr>
<td></td>
<td>Stimulated ‘natural killer’ activity</td>
</tr>
</tbody>
</table>

Fig. 17

Effect of oral N-acetylcysteine (NAC) 600mg/day on markers of immune function.

Percentage change from baseline in immune function values in postmenopausal women receiving oral NAC 600mg/day for 2 months. Values are shown for the combined treatment groups and in groups stratified by age (50-60 years and > 70 years).

IL = interleukin; NK = natural killer; PHA = phytohemagglutinin; SO = superoxide; TNF = tumour necrosis factor-α. All changes from baseline were significant (p ≤ 0.05).
9. Tolerability

9.1 General Profile
Oral NAC has a general tolerability profile similar to that of placebo.[40,74] Adverse events occur infrequently, are generally mild in severity and resolve without medical intervention. When they do occur, adverse events include gastrointestinal effects (e.g., pyrosis, nausea, vomiting, and diarrhea), headache, fever, and hypersensitivity reactions (e.g., urticaria).[25]

In a summary of tolerability data from nine randomized, controlled clinical trials of oral NAC 300–600mg/day administered for 6 to 180 days in adults or children with respiratory conditions,[74] there was no difference between NAC and placebo in the incidence of adverse events (based on adverse events leading to the withdrawal of treatment). These events were generally gastrointestinal in nature (gastric pyrosis, nausea, dyspepsia, diarrhea, stypsis, and rarely vomiting). The exceptions to gastrointestinal events were urticaria and itching in one patient receiving NAC and two patients receiving placebo. Similar results were shown in a meta-analysis of 23 randomized, controlled trials of oral mucolytic drugs, primarily NAC, in patients with stable bronchitis or COPD.[41] The frequency of adverse events was similar between mucolytic and placebo recipients.

The frequency of adverse events suspected to be associated with oral NAC have been estimated from spontaneous or solicited reports from physicians in clinical practice in Europe (table X).[74]

Table X  Adverse events possibly associated with oral N-acetylcysteine (NAC) based on reports by prescribing physicians in Europe[74]

<table>
<thead>
<tr>
<th>Rating</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional (1–10% of patients)</td>
<td>Gastric events (pyrosis, nausea), intestinal events (diarrhea, stypsis) and dyspepsia</td>
</tr>
<tr>
<td>Rare (&lt;1% of patients)</td>
<td>Urticaria/itching, anorexia, vomiting, abdominal distension and dizziness/malaise</td>
</tr>
<tr>
<td>Once only</td>
<td>Asthma worsening, dyspnea and lessening of phenprocoumon effects</td>
</tr>
<tr>
<td>Once only but causal association with NAC deemed unlikely by reporting physicians</td>
<td>Alopecia and menorrhagia</td>
</tr>
</tbody>
</table>

The once-daily effervescent tablet formulation of NAC 600mg is at least as effective and well tolerated as NAC 200mg three times daily.[74] Higher dosages of NAC than those commonly used as mucolytics are also well tolerated.[74] In the study of oral NAC as an influenza prophylactic, the proportion of patients reporting adverse events was not significantly different between NAC 600mg twice daily and placebo (9% vs 5%).[25] Moreover, there were no significant differences between treatment groups for any of the individual adverse events. Oral NAC is also well tolerated in children.[46] In the study in children with obstructive bronchial diseases,[46] oral NAC was well tolerated by 96% of patients (64 of 67 patients reported good acceptance and safety). Only three patients (4%) had minor adverse effects, and all patients considered there were no safety issues.

Table XI  Laboratory indices that were not changed following treatment with oral N-acetylcysteine in clinical trials in patients with respiratory conditions or in healthy volunteers[74]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation</td>
<td>Prothrombin, thrombin, Factors VII and X, fibrinogen, platelet aggregation</td>
</tr>
<tr>
<td>Hematological</td>
<td>Hematocrit, hemoglobin, red blood cells, white blood cells, platelets, erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, orthonine carbamyl transferase, bilirubin</td>
</tr>
<tr>
<td>Fecal</td>
<td>Occult blood</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Serum IgA, IgG, IgM, sputum IgA</td>
</tr>
<tr>
<td>Other blood chemistry</td>
<td>Serum protein fractions, cholesterol, glucose</td>
</tr>
<tr>
<td>Renal</td>
<td>Blood urea nitrogen, serum creatinine, urinalysis</td>
</tr>
</tbody>
</table>
9.2 Gastrointestinal Events

Although most adverse events are gastrointestinal in nature, therapeutic doses of oral NAC do not cause a loss of blood in the gastrointestinal tract. Moreover, oral NAC taken on a full or empty stomach does not adversely affect the stomach or duodenum as assessed by gastroduodenal endoscopy or histological examination. In a placebo-controlled endoscopic study of therapeutic dosages of oral NAC (200mg two to three times daily for 14 days) in patients with bronchopneumopathies, NAC was not associated with any gastroduodenal lesions (edema, hyperemia, erosions or ulcerations) or pathological changes.

9.3 Laboratory Parameters

Oral NAC was not associated with changes in values of laboratory tests in clinical trials in patients with respiratory conditions (table XI). Oral NAC did not affect hematological, coagulation, platelet aggregation, hepatic, renal, immunoglobulin, serum protein fractions, cholesterol or glucose values.
10. Dosage and Administration

Oral NAC is indicated in acute respiratory conditions associated with cough (e.g. productive cough, acute bronchitis and influenza; figure 1). It reduces the viscosity and facilitates expulsion of mucous secretions and has a protective action on the respiratory system. NAC is available as an over-the-counter product in the form of granules or effervescent tablets for oral solution, and oral solution. A summary of product information is presented in table XII.

Table XII Summary of product information for oral N-acetylcysteine (NAC)

| Indications for use in respiratory conditions | Respiratory conditions characterized by the formation of dense, difficult-to-expectorate secretions |
| Mechanism of action | Mucolytic, antioxidant and anti-inflammatory |
| Usual dosage in acute conditions | 300-600mg/day |
| Children (aged 2–12y) | 600mg/day divided into one or more administrations (e.g. 200mg three times daily or 600mg as a single dose) |
| Adults | 600mg/day divided into one or more administrations (e.g. 200mg three times daily or 600mg as a single dose) |
| Adverse effects | Occur rarely |
| Gastrointestinal effects: pyrosis, nausea, vomiting, diarrhea |
| Other: urticaria, headache, fever |
| Predisposed patients: hypersensitivity reactions (e.g. urticaria, bronchospasm) |
| Unpleasant breath odor: probably due to the breaking of mucous disulfide bonds |
| Contraindications | Hypersensitivity to any of the ingredients |
| All formulations | Active gastroduodenal ulcer |
| Granules and effervescent tablets | Phenylketonuria: these formulations contain aspartame (as an excipient), which metabolizes to phenylalanine |
| Granules | Fructose intolerance: this formulation contains sorbitol (as an excipient), which metabolizes to fructose |
| Ready-to-use syrup | Confirmed hypersensitivity to preservative agents E218 or E211: this formulation contains E218 and E211 |
| Precautions | Asthma, a past history of bronchospasm or other serious respiratory insufficiency, as NAC may increase obstruction of the respiratory tract or induce bronchospasm |
| Risk of gastrointestinal bleeding (e.g. history of peptic ulceration or esophagus varices), as oral NAC may induce vomiting |
| Pregnancy: animal studies did not show any teratogenic effects, but the administration of NAC during pregnancy must be supervised by a physician |
| Breast feeding: there is a lack of data on the passage of NAC into breast milk, however discontinuation of lactation is advised when receiving NAC therapy |
| Effervescent tablets | Hypertension or other conditions in which salt use is to be avoided: this formulation contains 140mg sodium (350mg sodium chloride); therefore, use one of the salt-free formulations |
| Potential drug interactions | Concomitant treatment with certain antibacterials or metal salts: a 2-hour interval should separate their administration |
| Availability | Granules for oral solution 100, 200 and 600mg sachets |
| Ready-to-use oral solution 2% (100mg/5mL) |
| Effervescent tablets for oral solution 200 and 600mg |
| Storage | All products Away from light in a dry place at room temperature |
| Ready-to-use-syrup after opening 15 days at room temperature |
11. Conclusions

The oral formulation of NAC is convenient and easy-to-use, and represents a useful option in the treatment of patients with acute respiratory conditions (figure 1). NAC safely and effectively reduces mucous and cough in adults and children with acute respiratory disorders. Its mucolytic effects in breaking disulfide bonds in mucous and enhancing mucociliary transport are useful in respiratory conditions associated with dense difficult-to-expectorate mucus. In addition, its antioxidant, anti-inflammatory, and immunomodulatory effects offer protection against inhaled oxidants, are beneficial in attenuating influenza-like symptoms and rejuvenate immune function of neutrophils and lymphocytes in older patients. An overall summary of the clinical benefits of the use of NAC in treating acute respiratory conditions is presented in table XIII.

Table XIII  Summary of the overall clinical benefits of oral N-acetylcysteine (NAC) in the treatment of acute respiratory conditions

- Mucolytic, antioxidant, anti-inflammatory and immunomodulatory effects
- Mucolytic effect involves decreasing mucous viscosity and improving mucociliary transport
- Antioxidant effects are both direct and indirect
- Anti-inflammatory effects involve antioxidant properties, re-establishment of the cellular reductive-oxidative equilibrium and preventing the release of inflammatory cytokines
- Immune effects involve antioxidant protection against oxidative stress and improving the function of some immune cells
- Effective in a wide range of acute respiratory disorders in adults and children
- May be used in combination with antibacterials in patients with acute respiratory infections with mucopurulent sputum
- Confers protection against cigarette smoking and air-borne pollution
- Decreases the severity and frequency of influenza-like symptoms in high-risk patients
- Restores age-related deterioration of immune function
- Very well tolerated in adults and children
- Tolerability profile similar to that of placebo
12. References

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