Ambroxol in the 21st century: pharmacological and clinical update

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Background: Belonging to the group of expectorants, ambroxol is an active substance with a long history that influences parameters considered to be the basis for the physiological production and the transport of the bronchial mucus. Therefore, ambroxol's indication is 'secretolytic therapy in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport'. *Objective*: The aim of this review is to evaluate the pharmacological and clinical data on the mucokinetic compound ambroxol. *Methods*: The existing database that covers > 40 years of pharmacological research and clinical development was analysed. Only studies with adequate study design were evaluated. *Conclusion*: Ambroxol is shown to exert several activities: i) secretolytic activity (i.e., promotes mucus clearance, facilitates expectoration, and eases productive cough); ii) anti-inflammatory and antioxidant activity; and iii) a local anaesthetic effect through sodium channel blocking at the level of the cell membrane. The reduction on chronic obstructive pulmonary disease exacerbations is consistent and clinically relevant. The anaesthetic effect is a new pharmacological action that could be beneficial in the management of acute respiratory tract infections. The efficacy and safety of ambroxol is well established.

Keywords: ambroxol, cough, expectorant, mucoactive drugs, mucus hyper-secretion, respiratory diseases

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1. Introduction

Airway mucus hyper-secretion is a feature of various respiratory diseases, including chronic bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchiectasis and asthma. The overt clinical symptoms of cough and expectoration, coupled with the concomitant perceived importance of mucus in the pathophysiology of many severe lung conditions, have led to development of drugs that affect respiratory mucus: the mucoactive agents [1]. The primary action of a mucoactive drug is the capability to modify mucus production, mucus composition and/or mucus interaction with the mucociliary epithelium.

A simple drug's classification system based on putative mechanisms of action includes expectorants, mucolytics, mucokinetics and mucoregulators [2]. Expectorants increase secretion of mucins and/or increase mucus hydration (ambroxol, guaifenesin, hypertonic saline); mucolytics reduce the viscosity of mucus (*N*-acetylcysteine, carbocysteine, dornase alfa or rhDNase). Mucokinetic agents increase mucus 'kinesis', effectively increasing the transportability of mucus by cough (β2-adrenoceptor agonist bronchodilators and surfactant).

Ambroxol, the eighth active metabolite of bromhexine, is a mucoactive agent endowed with stimulating effects on the mucociliary clearance. Ambroxol has been widely studied for clinical use to assess its effectiveness in respiratory diseases

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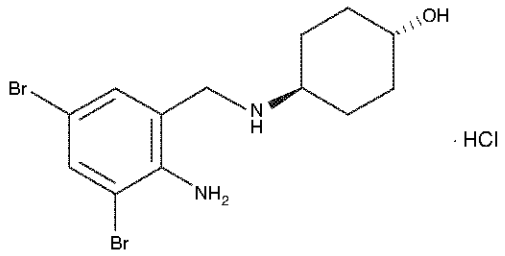

$C_{13}H_{19}Br_2ClN_2O$

characterised by airway mucus hyper-secretion such as COPD [3] and prevention of chronic bronchitis exacerbations [4-8]. The use of ambroxol is also reported for the management of CF [9,10], for the prevention and treatment of hyaline membrane disease in newborns [11,12], in the treatment of bronchial asthma and spastic bronchitis [13], in antioxidant therapy [14], for the prevention of bronchopulmonary complications after chest surgery [15], in the treatment of selected diseases of the upper respiratory tract [16] and in pulmonary alveolar proteinosis [17].

2. Introduction to the compound

Ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$, CAS No. 23828-92-4), a substituted benzylamine, is an active *N*-desmethyl metabolite of bromhexine hydrochloride (2-amino-3,5-dibromo-*N*-methylbenzylamine hydrochloride), which is itself a synthetic derivative of vasicine, the active principle extracted from the plant species *Adhatoda vasica*. Ambroxol differs from bromhexine in the absence of a methyl group and the introduction of a hydroxyl group in a para-trans position of the cyclohexyl ring.

3. Primary pharmacology of ambroxol

The mechanisms of action of Ambroxol have been extensively investigated and comprise mucokinetic properties [18], mucociliary activity [18], stimulation of surfactant production [19,20], anti-inflammatory and antioxidative actions [21] and the local anaesthetic effect [22,23].

3.1 Mucokinetic properties

In anaesthetised rabbits and guinea-pigs, ambroxol hydrochloride significantly increased bronchial secretions in a dose-dependent fashion [24].

Furthermore, ambroxol significantly increased the respiratory tract fluid volume in rabbits up to 9 h after administration of the drug [25]. In ferrets, ambroxol when administered intratracheally, increased mucous glycoprotein secretion dose-dependently [26].

3.2 Mucociliary activity

In isolated lung preparations of rat, hamster and cat airways, ambroxol stimulated ciliary activity [27]. In addition, a significant increase of ciliary beat frequency was found in isolated tracheal cells of guinea-pigs [18]. In an *in situ* frog oesophageal preparation, a dose-related increase in the rate of particle transport was demonstrated after topical application of ambroxol [28].

3.3 Stimulation of surfactant

Compared with other mucolytic agents, additional properties could be demonstrated for ambroxol, as it also activates the surfactant system of the lung. A surfactant is believed to act as an antiglue factor in the alveoli and bronchi and prevent secretions from sticking to the walls of the bronchial tree, thus facilitating mucus transport [29]. Ambroxol stimulates the production of surfactant in alveolar type II cells [30]. This is reflected by increased incorporation of labelled precursors into alveolar phosphatidylcholine and by enhanced storage of lamellar bodies in type II cells. Upregulation of surfactant levels may be a principal defence mechanism against influenza A virus infection [31]. In rats treated with ambroxol at doses of 100 and 200 mg/kg p.o. for 3 or 6 days, a rapid rise in the volume of type II epithelial cells in the lungs was observed, and the ratio of lamellated bodies with respect to alveolar tissue increased significantly [32]. Treatment of rats with ambroxol (200 mg/kg/day p.o.) resulted in an increased incorporation of tritiated palmitic acid into alveolar tissue, which is consistent with an increase in the synthesis of the pulmonary surfactant [33,34].

In addition, histochemical quantification of phospholipids in the lungs of rats by image analysis [35] revealed that treatment with ambroxol (50 mg/kg intra-peritoneally b.i.d. for 3.5 days) significantly increased the area stained for phospholipids in the lungs compared with controls.

Stimulation of surfactant production was also demonstrated in fetuses and premature animals. Treatment of pregnant rabbits with ambroxol (50 mg/kg i.v.) on days 24 – 26 of gestation resulted in an improved lung function in the prematurely delivered fetuses [36]. Likewise, antenatal treatment of prematurely delivered rabbits with ambroxol led to enhanced alveolar expansion [37]. Furthermore, administration of 4 mg/kg/day ambroxol to pregnant does on days 21 – 24 of gestation resulted in significant enhancement of lung maturation in the 25-day fetal rabbit lung [38].

The efficacy of ambroxol was also demonstrated in an animal model of adult respiratory distress syndrome. Adult respiratory distress syndrome was induced in minipigs by hydrochloric acid aspiration. Treatment with ambroxol resulted in the survival of all treated animals, whereas all animals of the control group died within 12 h [39].

3.4 Antioxidative/anti-inflammatory activities

The antioxidant properties of ambroxol as a free radical scavenger are well established and documented in several studies [40-44], suggesting protection against oxidative stress by free radicals as derived from tobacco smoke, other toxic inhalants and also from the activity of inflammatory

cells such as neutrophils and alveolar macrophages [45]. Likewise, ambroxol was shown to protect against lipid peroxidation in the heart of mice induced by cytotoxic agents (i.e., doxorubicin) [46].

Anti-inflammatory properties of ambroxol were demonstrated in several studies using neutrophils, macrophages and mast cells. Ambroxol is endowed with the capacity to interfere with oxidative and proteolytic histotoxic activities of neutrophils by acting at multiple levels. In particular, ambroxol is able to inhibit production of superoxide anion and hypochlorus acid (HOCl), curb the exocytosis of elastase and myeloperoxidase-positive primary granules, impair the production of HOCl by decreasing the availability of myeloperoxidase, scavenge HOCl directly and protect α-1 antitrypsin from neutrophil-mediated inactivation, and in turn restore the capacity of the antiprotease to complex and inactivate elastase [47].

Ambroxol significantly decreased the lipopolysaccharide (LPS)-induced synthesis of cytokines in rat alveolar macrophages, attenuated the LPS-stimulated superoxide anion and hydrogen peroxide production, and significantly decreased the LPS-induced nitric oxide production [48,49].

Ambroxol strikingly reduced histamine and growth factor release from human mast cells and monocytes, respectively, which are located in large numbers in the lung, skin and intestines. These cells are primarily responsible for mediating the acute phase of immediate hypersensitivity reactions particularly owing to the release of histamine, which causes smooth muscle contraction, vasodilatation and increased vascular permeability. As ambroxol has been shown to reduce bronchoconstriction, the results provide a mode of action of this drug attributable to its inhibitory action on histamine release as well as leukotriene synthesis [50-53].

The anti-inflammatory properties of ambroxol were further explored in an acute lung injury model. Ambroxol reduced LPS-induced lung haemorrhage, oedema, exudation and neutrophil infiltration. Furthermore, protein concentration, TNF-α, IL-6, and TGF-β1 were significantly reduced in the broncho-alveolar lavage by treatment with ambroxol [54]. Consistently, several studies demonstrated the protective effect of ambroxol in lung cells or on pulmonary tissues [55-57].

In an influenza virus infection model in mice, ambroxol suppressed virus multiplication in the airway fluid and significantly improved the survival rate of mice infected with influenza A virus; however, the mechanism of action is not clear and needs to be further elucidated [58].

3.5 Local anaesthetic effect

The local anaesthetic properties of ambroxol were described first in 1977 but only recently the underlying molecular mechanism has been explained. Ambroxol was identified as a very potent inhibitor of the neuronal voltage-gated Na^+ channel [22,23].

4. Non-clinical drug safety

A broad range of toxicity studies with ambroxol hyrdochloride was performed between 1973 and 1986 according to the state-of-the-art at that time, before the GLP- and ICH-era. Nevertheless, all currently required toxicity end points including safety pharmacology according to ICH S7A and S7B were adequately addressed and the conclusions are considered valid.

The acute oral, intravenous, subcutaneous and intraperitoneal toxicity of ambroxol in mouse, rat, rabbit, guinea-pig and dog is low [24,59,60]. The main signs of toxicity following overdosing across species were dyspnoea, ataxia and partly tonic-clonic convulsions. Subacute and chronic oral toxicity studies in rats (52 and 78 weeks), rabbits (26 weeks) and dogs (52 weeks) did not result in any serious functional adverse effects or distinct target organ toxicity up to 2500 mg/kg (rat) and 250 mg/kg (rabbit and dog). All observed adverse effects were reversible as shown by the recovery groups [60-63]. The 'no observed adverse effect levels' were 50 mg/kg (rat), 40 mg/kg (rabbit) and 10 mg/kg (dog). Four-week intravenous toxicity studies with ambroxol in rats using 4, 14 and 64 mg/kg and in dogs using 45, 90 and 120 mg/kg (three infusions) showed no marked local and systemic toxicity including histopathology. Ambroxol was not embryotoxic and teratogenic at oral doses up to 3000 mg/kg in rats and 200 mg/kg in rabbits [64]. Furthermore, it did not impair fertility and postnatal development [65,66]. Ambroxol was not mutagenic in the Ames and mouse bone marrow micronucleus test. There was no tumorigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg) and rats (65, 250 and 1000 mg/kg) when treated with a diet for 105 and 116 weeks, respectively. Overall, ambroxol is a thoroughly examined drug with a well-established favourable safety profile in animals, which is confirmed by the large-scale therapeutic use in humans.

5. Clinical pharmacokinetics and metabolism

Ambroxol is marketed in various pharmaceutical formulations, including intravenous and intramuscular solutions, liquids, granules, tablets, capsules, suppositories and oral slow release formulations. After intravenous infusion, the total plasma clearance is 660 ml/min, to which renal clearance (53 ml/min) contributes only 8% [67]. Because the volume of distribution is high (about 560 l, with > 17-fold accumulation in the lung compared with plasma) [68], the elimination half-life is quite long (10 h). The absolute bioavailability after oral tablet dosing is 79%, and dose proportionality has been demonstrated from 30 mg up to 500 mg oral tablet doses in steady state. Absorption is rapid, with T_{max} ~ 1.6 h. The plasma protein binding is 90% [69]. Ambroxol is predominantly eliminated by biotransformation, the principal Phase I metabolite being dibromoanthranilic acid. Phase II metabolic reactions also occur, yielding glucuronides [70]. It was shown

that cytochrome P450 3A4 is predominantly responsible for oxidative metabolism of ambroxol [71]. However, no significant drug–drug interactions with ambroxol have been reported.

6. Clinical efficacy and safety

When analysing the clinical data on mucoactive substances it should be taken into account that the vast majority were generated > 40 years ago when guidelines on good clinical practice were not in place. The understanding of the mechanisms involved in respiratory diseases associated with cough and expectoration was at its infancy and there was lack of agreement on a definition of chronic respiratory diseases such as chronic bronchitis, COPD, emphysema and asthma [72].

Chronic cough and expectoration were recognised as having an impact only on morbidity and mortality in the mid-1990s [73]. This study showed that in subjects reporting mucus hyper-secretion at the initial examination, pulmonary infection was implicated in 54% of deaths, whereas this occurred only in 28% of patients without mucus hyper-secretion. Chronic mucus hyper-secretion was found to be a significant predictor of COPD-related death with associated pulmonary infection (relative risk: 3.5) but not of death without pulmonary infection (relative risk: 0.9). These findings changed how the efficacy of mucoactive drugs had to be evaluated. The impact on acute exacerbations of COPD and health status/quality of life were considered primary end points instead of lung function tests (LFTs).

Out of the total ambroxol database, 92 studies could be considered of acceptable quality and could be used for evaluating the clinical efficacy of ambroxol in the management of acute and chronic lower respiratory diseases in adults and children.

6.1 Efficacy in adults

The studies were classified as short-term (< 2 weeks duration) and long-term (> 4 weeks duration) studies. Based on acceptability of study design (randomised, double-blind, placebo or active controlled) 3 out of 24 short-term studies and 7 out of 12 long-term studies were evaluated and have been included in this overview. The other 68 studies were not included because of poor study design (open, uncontrolled, small number of patients, single dose). Although positive results were reported in most studies, we felt that owing to the poor design these trials should not be included in the evaluation.

6.1.1 Short-term studies

Primary end points in short-term studies focused on respiratory symptoms, quantity/quality of mucus and severity of cough, difficulty of expectoration and LFT (forced expiratory volume in 1 sec [FEV_1], peak expiratory flow rate (PEFR)).

Three studies showed clinical efficacy as improvement in respiratory symptoms, that is, ease of expectoration, phlegm loosening [74], decrease in sputum volume and sputum viscosity [75], and reduction in the rate of non-responders [76].

LFT was performed in all the studies and as expected ambroxol had no effect on either FEV_1 or PEFR [74-76]. Similar to the study conducted by Germouty and Jirou-Najou [75] in which ambroxol was given together with an antibiotic and achieved clinical efficacy compared with placebo, it is of interest to note that several studies have shown that ambroxol enhances the therapeutic effect when given in combination with antibiotics. This is due to its ability to increase antibiotic levels in lung tissue and mucus, which is a unique feature of this mucoactive substance [77,78].

The effect of short-term administration of ambroxol on lung mucociliary clearance has been studied mainly in patients with COPD who had severely impaired mucociliary clearance [79]. Details of the studies are summarised in **Table 1**.

Even in patients with markedly abnormal lung clearance, ambroxol showed an improvement, albeit modest. It is of interest to note that in the studies that investigated penetration index (i.e., how far the inhaled radioactive particles were deposited in the airways), ambroxol was shown to increase the penetration index. These findings suggest that ambroxol has an effect on small airways obstruction probably by increasing clearance of secretion. A similar effect on penetration index has been reported with bromhexine but other mucolytics drugs, such as guaphenesin, 2-mercapto-ethane-sulfonate and *N*-acetyl cysteine (NAC), have failed to show this effect.

6.1.2 Long-term studies

Five studies were randomised, double-blind, placebo-controlled [7,80-83], one was randomised active controlled [84] and one was open [85].

In five out of seven studies, the duration of treatment was at least 6 months and the primary end point in four studies was related to the incidence of acute exacerbations and loss of work days [7,80-82]. Secondary end points included sputum volume, physical properties, symptoms (cough and expectoration) as well as LFT. Incidence of exacerbations was a secondary end point in one study [82]. The daily dose of ambroxol was 75 mg in studies of at least 6 months duration and 120 mg in the two studies of 4 weeks duration.

In studies with a duration of treatment of at least 6 months, a reduction in the incidence of acute exacerbations and/or days off work was observed [7,80-82,85]. It is of interest to note that ambroxol significantly reduced exacerbations particularly in patients with more severe disease at baseline [7,85]. In the AMETHIST study [7] corticosteroids were discontinued during the study. This is clinically relevant as several studies conducted in patients with COPD have shown that a reduction in acute exacerbations is associated with a lower number of days off work, as well as number of hospital

Table 1. Ambroxol-lung mucociliary studies.

Drug/dose	LMC	Aerosol penetration	Ref.
Mucosolvan 90 mg	Small effect only at 60 min compared with placebo		[79]
Mucosolvan 90 mg/day + clenbuterol	Effective in only 1 out of 5 regions	Improvement	[79]
Mucosolvan 90 mg/day + theophylline	Small but significant effect		[106]
Mucosolvan 120 mg/day	No effect		[107]
Bromhexine 16 mg t.i.d. × 2 weeks	Enhancement	Improvement	[108-110]
Bromhexine i.v. single dose	No effect	N/A	[111]
Guaphenesin single dose	No effect	No effect	[108]
2-Mercapto-ethane-sulfonate aerosol	Effect on LMC = hypertonic saline	No effect	[108]

LMC: Lung mucociliary clearance; t.i.d.: Ter in die.

admissions [4,6,8]. It is well documented that exacerbations are the key cost drivers of COPD [86].

LFTs were included in two studies as primary end points and in five studies as secondary end points; no improvement in LFT was shown in any of the studies.

Health related quality of life (QoL) was investigated as a secondary end point by Guyatt *et al.* [83]. Ambroxol had no effect on the symptoms domain of the QoL questionnaire used in this study.

Although the study was well designed in terms of study design (inclusion/exclusion criteria) and statistical methods, it had some flaws. The sample size for the symptom questionnaire was based on an assumption as no data were available to calculate an adequate sample size. It is possible that the sample size, although adequate for LFTs, was too small for the symptom questionnaire. A major deficiency of the study was that the duration was too short for the symptom questionnaire.

The effect of highly effective treatment interventions such as short- and long-acting bronchodilators or inhaled steroids have failed to show a significant increase in baseline FEV_1 [87-91]. The lack of effect of ambroxol on respiratory symptoms is due to the fact that the duration of treatment was too short. It is well recognised that when investigating the effect of treatment interventions (i.e., bronchodilators, inhaled steroids) on disease specific outcomes, the duration of the study is at least 3 months and in most studies was at least 1 year.

It is possible that more specific questionnaires related to cough and expectoration need to be designed to evaluate the effect of mucoactive drugs.

6.2 Efficacy in children

Most of the studies were conducted according to an open design in children with acute respiratory disorders (i.e., bronchitis and tracheobronchitis) [92-95], bronchial hyper-reactivity [96], CF [97] and ENT (ear, nose and throat) diseases such as sero-mucous otitis [98] and inflammation of paranasal sinuses [99]. The efficacy and safety of different formulations of ambroxol have been established in children aged 10 months to 12 years [100].

Three comparative studies versus NAC showed that both drugs were effective in improving symptoms (cough and expectoration) but ambroxol was either more effective [95] or had a more rapid effect than NAC [94]. Principi *et al.* studied the interaction of ambroxol and antibiotics (amoxicillin, ampicillin, erythromycin) in children with acute lower respiratory tract infection. A significant clinical and radiological improvement was observed in the ambroxol and antibiotics group compared with antibiotics alone [93].

The study in CF [97] was only a pilot study and although ambroxol was superior to NAC and bromhexine no conclusions can be drawn on the efficacy of ambroxol in CF.

Although ambroxol is not registered for ENT indications, a study conducted in children with otitis media [98] showed that ambroxol improved objective measurements (e.g., opacity of the tympanum membrane, tympanogram, hypoacusia) as well as clinical symptoms (e.g., feeling of occlusion of ears, difficulty in breathing and rhinorrhoea). In children with inflammation of paranasal sinuses, treatment with ambroxol was associated with a shortening of duration of anti-inflammatory and antibiotic treatment [99].

6.3 Efficacy in sore throat treatment – local anaesthetic activity

Ambroxol's local anaesthetic activity [22,23] was investigated in randomised, placebo-controlled, clinical trials in adult patients with acute, uncomplicated sore throat of recent onset without signs or symptoms of bacterial infection. Ambroxol

was used in concentrations of 20 and 30 mg/lozenge. The efficacy of sore throat treatment was evaluated at the levels of 'pain intensity' (3 h response to a first lozenge) and 'ability to reduce pain effectively' (pain relief during subsequent ambulatory treatment with up to six lozenges/day, 30 min intervals). At each time point, efficacy was recorded by a verbal rating scale. Ambroxol lozenges proved statistically superior to placebo with regard to the extent and duration of the reduction in pain intensity after a first lozenge with effects observed up to 3 h after dosing. The 30 mg ambroxol lozenges were not superior to the 20 mg lozenges. Hence, lozenges containing 20 mg ambroxol were found to represent an efficacious, safe and well-tolerated short-term therapy for the relief of sore throat [101,102].

Further clinical data refer to a pharmacy-based observational study, also known as postmarketing surveillance (PMS), which is an accepted tool for medicinal product research [103]. A PMS for ambroxol cough syrup (Mucosolvan™, Boehringer Ingelheim) was conducted with 2664 evaluated participants in 266 German pharmacies. The study protocol included patients who had spontaneously requested the product from the pharmacy. Surprisingly, the results of this PMS revealed a range of actions one would not necessarily associate with a mucoactive substance such as soothes cough irritation in the throat (43%), soothes irritated sites in the throat (15%), relieves soreness in the throat (28%) [104].

6.4 Clinical safety

Ambroxol has been available in the market since 1973 and its safety is based on its use in > 15,000 patients in > 100 studies and an estimated total of 4,789,563 patient-years in the most recent Periodic Safety Update Report. Skin rashes, nausea and vomiting, abdominal pain, dyspepsia, anaphylactic reactions, and allergic reactions were the most prominent reports. Ambroxol can be accepted to be generally safe and well tolerated in adults and children.

7. Conclusion

Ambroxol is well documented and well established in secretolytic therapy in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport. Ambroxol exerts secretolytic, mucolytic, secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract, hence preventing impaction of viscous secretions and reducing the impedance of cavitary and broncho-alveolary aeration. By this means, ambroxol is able to restore and/or improve host defence against infection (natural defences). Furthermore, ambroxol exerts anti-inflammatory and antioxidant actions that are beneficial in balancing inflammatory reactions to alleviate symptoms of cough and cold. It also exerts a local anaesthetic effect, which makes it an efficacious treatment for sore throat.

Ambroxol has been extensively investigated in various forms of acute and chronic inflammatory diseases of the upper and lower respiratory tract, in particular bronchitis. Several of these studies were conducted well before the implementation of the principles of good clinical practice. Not all studies are well documented. These studies, however, generally provide evidence of a beneficial impact on the symptoms of such inflammatory diseases. In chronic bronchitis, ambroxol relieves lead symptoms (cough, difficulty to expectorate) and helps to prevent acute exacerbations. In uncomplicated acute bronchitis, ambroxol supports the otherwise spontaneous regression of the disease, promoting a relatively faster and more complete recovery with less incapacitation.

8. Expert opinion

The pharmacodynamic and pharmacokinetic profile of ambroxol, together with safety and efficacy evidence from clinical trials, shows that it represents a valid treatment of diseases of the respiratory tract. Several diseases including chronic bronchitis, COPD and CF exhibit characteristics of airway mucus hyper-secretion leading to pathophysiological sequelae of clinical concern such as bacterial colonisation, repeated chest infections and exacerbations, which are associated with morbidity and mortality. Ambroxol is a mucoactive drug with several properties that are particularly useful under these circumstances, including secretolytic and secretomotoric actions, which restore the physiological clearance mechanisms of the respiratory tract and play an important role in the body's natural defence mechanisms. Ambroxol stimulates synthesis and release of surfactant by type II pneumocytes. Several studies have demonstrated the importance of surfactant in reducing the adhesion of mucus to the bronchial wall, improving its transport, and in providing protection against bacterial aggression and irritating agents. In addition, ambroxol is able to alleviate symptoms by its anti-inflammatory and antioxidant action. By showing a local anaesthetic effect, ambroxol has proved to offer an efficacious treatment for sore throat.

Many studies have evaluated the clinical efficacy of ambroxol in the management of acute and chronic lower respiratory diseases in children and adults. The efficacy and safety of ambroxol has been established in children suffering from acute respiratory disorders (i.e., bronchitis, bronchial hyper-reactivity, CF) and diseases such as sero-mucous otitis and inflammation of paranasal sinuses. Ambroxol proved to be effective in improving symptoms, which led to a shortening of duration of anti-inflammatory and antibiotic treatment. Among adults, primary end points in some short-term studies focused on respiratory symptoms, quantity/quality of mucus and severity of cough, difficulty of expectoration and LFT (FEV_1 and PEFR). Therapeutic efficacy was demonstrated as improvement in respiratory symptoms and decrease in sputum volume and sputum viscosity. As expected, ambroxol had no

effect on either FEV_1 or PEFR. Ambroxol also increases lung tissue levels of some antibiotics.

Long-term ambroxol treatment of at least 6 months was found to reduce the incidence of acute exacerbations and/or days off work. In this regard, we conducted a large, double-blind, long-term, multi-centre study (The AMETHIST Trial) [7] comparing oral ambroxol with placebo in 234 patients with COPD treated for 12 months. The results showed that taking 75 mg ambroxol b.i.d. is not different from placebo in preventing acute exacerbations; however, in the subset of patients with a more severe disease at baseline, ambroxol showed a significant difference in cumulative exacerbation-free persistence, suggesting that the beneficial effects of secretolytic drugs are more obvious in patients with severe cough and difficulty of expectoration than in patients with mild disease. This finding indicates that particularly patients with viscous sputum and frequent exacerbations benefit from ambroxol treatment. In studies conducted with long-acting bronchodilators and/or inhaled steroids a reduction in exacerbations of 20 – 25% is considered clinically relevant [91]. In the AMETHIST study, the subset population analysis showed that the percentage of patients with exacerbations in the ambroxol-treated group was 38% whereas in the placebo group it was 63%, the difference between placebo and ambroxol being statistically significant and clinically relevant. Recent published guidelines for the management of COPD (GOLD 2007) support this observation [105].

Ambroxol's local anaesthetic activity was demonstrated in randomised, placebo-controlled, clinical trials in adult patients with acute, uncomplicated sore throat showing that lozenges containing 20 mg ambroxol represent an efficacious, safe and well-tolerated treatment for the relief of acute sore throat. More recent clinical data refer to a pharmacy-based observational study, also known as PMS, which is an accepted tool for medicinal product research [103]. This PMS demonstrated that ambroxol cough syrup effectively combines the principles of demulcent and local anaesthesia leading to the relief of pharyngeal cough beside its mucoactive effect. It is known that demulcents are effective, although to a limited extent, mainly in postinfectious irritative cough (and sore throat) when cough receptors usually become hypersensitive. However, this requires an appropriate pharmaceutical formulation and type of use.

An extensive database is available on the safety and tolerability of ambroxol. The drug is accepted to be safe and well tolerated. Eventual adverse events are well known and related cautions and warnings are well established.

In conclusion, the mechanisms of action and the pharmacological effects of ambroxol have been widely investigated and several therapeutically important properties of this compound have been identified. Ambroxol's most significant therapeutic target is treatment of cough, which is also supported by current guidelines. In addition, more recent results show that long-term treatment with ambroxol is able to prevent exacerbations in COPD patients. Treatment with ambroxol was particularly efficient in those patients showing more marked respiratory symptoms and a strong history of frequent exacerbations.

Attempts to re-evaluate therapeutic effectiveness of secretolytic/mucoactive agents would generally be desirable. This could be achieved by the use of more suitable protocol designs, patient populations, target parameters and questionnaires. Based on ambroxol's multi-factorial properties, future clinical trials may also focus on the assessment of additional therapeutic indications as such strategies already led to the discovery of a treatment for sore throat.

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Declaration of interest

The authors have no conflict of interest to declare.

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