Mucoactive Agents in the Therapy of Upper Respiratory Airways Infections: Fair to Describe Them Just as Mucoactive?

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ABSTRACT

BACKGROUND: Upper and lower respiratory tract infections are common conditions for which medical advice is sought, and their management relies on the use of prescription and over-the-counter (OTC) medicines. Ambroxol, bromhexine, carbocysteine, erdosteine, *N*-acetyl cysteine (NAC), and sobrerol are mucoactive agents for which clinical trials have been conducted, have been awarded well-established status by regulatory authorities, and are available as OTC or prescription products.

OBJECTIVE: To briefly review the evidence-based efficacy and safety of these substances in the therapy of upper respiratory airways infections.

METHODS: We conducted searches in MEDLINE and other databases for clinical trials and reviews done on the efficacy and safety of ambroxol, bromhexine, carbocysteine, erdosteine, NAC, and sobrerol.

RESULTS: Clinical trials have shown that these mucolytics have an important place in the relief of cough symptoms by easing the elimination of mucus. All drugs have shown comparable efficacy in the symptomatic treatment of productive cough, with some shared characteristics and some specific features.

CONCLUSIONS AND RELEVANCE: All mucolytics reviewed have a good safety profile, although some precautions should be taken when using ambroxol and bromhexine, and the use of NAC and carbocysteine should be monitored in special patient groups. Overall, however, the available evidence from randomised, controlled, and observational trials, as well as pragmatic, real-life experience, suggests that these products are useful in the therapy of upper respiratory airways infections, including bronchitis, sinusitis, and rhinosinusitis.

KEYWORDS: Ambroxol, bromhexine, carbocysteine, erdosteine, expectorants, mucokinetics, mucolytics, *N*-acetyl cysteine, sobrerol

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Background

Respiratory tract diseases affect a large number of people worldwide: in the European Union (EU), for instance, 7% of hospital admissions are linked to respiratory illnesses, which are responsible for approximately 12% of all-cause deaths.[1]

Upper and lower respiratory tract infections (RTIs) are common conditions for which medical advice is regularly sought, and their management relies on the use of prescription and over-the-counter (OTC) medicines.[2] Economically, RTI treatment is linked to significant expenses: in 2011, chronic obstructive pulmonary disease (COPD) and asthma, in the EU, caused €42.8 billion in direct (primary care, hospital outpatient and inpatient care, drugs, and oxygen) costs; indirect costs (lost production including work absence and early retirement) amounted to €39.5 billion.[3]

Mucoactive drugs are regularly used as a therapeutic option for mucus alterations, including hypersecretion. Mucus-thinning (mucolytics), cough-inducing (expectorants), and cough transport facilitating (mucokinetics) drugs have been available for clinical use to ease airway clearance in diverse indications such as bronchiectasis, COPD, acute, and chronic bronchitis or simply to relieve symptoms of acute cough caused by RTI.[4] The effects of these drugs in the treatment of various acute and chronic inflammatory diseases of the upper and lower respiratory tract have been investigated in a large number of clinical studies, which, however, were designed and conducted well before the principles of Good Clinical Practice were established. Many trials were open and non-controlled, and only relatively few randomised controlled trials (RCTs) are available for each individual drug in each indication. For erdosteine and *N*-acetyl cysteine (NAC), however, well-designed, blinded, placebo-controlled trials have recently shown a reduction in the frequency and duration of exacerbations in patients with COPD.[5–10]

In the past years, a number of systematic reviews have been published on the use of mucoactive agents in chronic bronchitis or COPD,[11] bronchiectasis,[12] acute cough,[13] or as an adjunct to antibiotics in acute pneumonia.[14] Almost all of them have concluded that mucolytics and mucokinetics have only a weak evidence-based support. The approach used in these reviews is scientifically sound and rigorous, but it reflects only the evidence provided by RCTs that were selected based on very

strict criteria. No consideration has been given to results of other RCTs, and open, prospective, or retrospective studies, or to patient's self-perceived and physician-assessed efficacy. In addition, all reviews are based on a very limited amount of studies and aggregate outcomes of trials conducted with different drugs.[11–14]

Ambroxol, bromhexine, carbocysteine, erdosteine, NAC, and sobrerol have all been awarded well-established status by regulatory authorities and are available as OTC or prescription products for selected indications. This work aims to evaluate the evidence-based efficacy and safety of these substances in the therapy of upper respiratory airways infections was provided not only by RCTs but also by observational studies.

Methods

We conducted searches in MEDLINE and other databases (search terms: antitussiv*, cough, productive cough, expectorant, mucolytic, ambroxol, bromhexine, carbocysteine, erdosteine, *N*-acetyl cysteine, sobrerol) for clinical trials and reviews on the efficacy and safety of these substances. No time limit has been set for the search.

We included in our evaluation RCTs and open, controlled, and uncontrolled trials with the aim to evaluate the reported efficacy and safety of these mucolytics with no restrictions on trial design. For products for which recent analyses have been published, we have considered all studies discussed in the reviews, but for the sake of brevity, we do not list or provide specific comments on individual trials unless needed. We did not limit the analysis to the proportion of participants who were cured but we considered also subjective and objective end points.

Ambroxol

Ambroxol exerts stimulating effects on mucociliary clearance and it increases cough effectiveness through its mucokinetic properties and stimulating surfactant secretion.[4] It has been available on the market for almost 50 years in several galenic forms, including ampules for parenteral use to treat the infant respiratory distress syndrome.

Physiologically, ambroxol has been shown to exert secretolytic, antioxidant, and anaesthetic activities.[15] This explains its usefulness in the prevention[16] and treatment of upper RTIs (URTI) associated with abnormal mucus secretion or impaired mucus transport. Its efficacy has been shown in more than 100 clinical observational, uncontrolled, or randomised, controlled, double-blind trials on more than 15 000 adult and paediatric patients with various forms of acute and chronic diseases of the upper and lower respiratory tract.[15] Animal and human studies have shown that ambroxol, administered concomitantly with amoxicillin, or ampicillin and erythromycin, increases the antibiotic levels in the lung.[17–20]

The product is safe,[15] although the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended to update the ambroxol product information by including the risk of allergic reactions and serious cutaneous adverse reactions.[21] Recently, a case of ambroxol-induced focal epileptic seizure in a patient with epilepsy has also been reported.[22]

To our knowledge, no interactions of ambroxol with other drugs have so far been demonstrated. The use of ambroxol in children younger than 2 years is not recommended.

Bromhexine

Bromhexine, like ambroxol, is available in several galenic formulations. Animal and human studies suggest that bromhexine influences mucus production, sputum quality and quantity, ciliary activity, and cough severity and frequency.[23] Zanasi et al[23] evaluated approximately 40 clinical studies conducted in patients with COPD, chronic or acute bronchitis, URTI and lower RTI, and bronchiectasis. The study designs ranged from observational, uncontrolled, to randomised, controlled, double-blind trials and included adults as well as children. Overall, bromhexine showed a modest efficacy, but its use was associated with a clinically consistent and subjectively perceived improvement in mucus clearance.[23]

As with ambroxol, antibiotic penetration seems to be enhanced by the concomitant administration of bromhexine.[24–26]

The safety of bromhexine has been demonstrated by clinical studies and long-term use, but the PRAC recommendations issued for ambroxol apply to bromhexine as well.[21] Bromhexine should not be used in children younger than 2 years.

Carbocysteine and NAC

N-acetyl cysteine and, to a lesser extent, carbocysteine (*S*-carboxymethyl-L-cysteine) are commonly prescribed as mucolytics in the treatment of COPD and bronchitis and are available as different galenic formulations. *N*-acetyl cysteine is also used in the management of paracetamol overdose.[27]

Cysteine derivatives have been shown in vitro to break disulphide bridges between the macromolecules present in the mucus, thus leading to a reduced mucus viscosity.[28] They are also endowed with antioxidant activities that, for instance, have been linked to their beneficial action in the pharmacologic treatment of COPD.[29–32] In adult patients with COPD or chronic bronchitis, both drugs cause a small reduction in acute exacerbations;[5,10,33,34] 2 studies have shown beneficial effects of carbocysteine on the quality of life of patients with COPD.[35,36] *N*-acetyl cysteine appears of no use in cystic fibrosis.[37] According to a review by Shen et al,[10] long-term high-dose NAC treatment may lead to a lower rate of exacerbations in patients with COPD.

Regarding paediatric patients with acute bronchopulmonary disease, a recent Cochrane review described the efficacy of both drugs as limited.[38]

N-acetyl cysteine and carbocysteine are generally recognised as safe in adults and children, but there have been reports

of respiratory paradoxical adverse drug reactions associated with their systemic use in paediatric patients.[39] Two case reports have suggested that carbocysteine may cause pneumonia in predisposed patients.[40,41] This would question the risk/benefit ratio of these drugs in children and in selected groups of patients.

Erdosteine

Erdosteine is a thiol derivative with mucolytic[42] and antioxidant activity.[43] It has been on the market for more than 20 years for the treatment of chronic obstructive bronchitis, including acute infective exacerbation of chronic bronchitis and COPD.[42,44] In clinical trials, erdosteine reduced frequency and severity of cough and sputum viscosity more effectively than placebo and was more efficient in reducing sputum adhesion than ambroxol.[44] Less (approximately 30) trials have been conducted with this drug than with the other mucolytics so far discussed,[45] but in recent well-designed, blinded, placebo-controlled trials, erdosteine has shown reduction in the frequency and duration of exacerbations in patients with COPD,[6–9] and, when administered concomitantly to standard treatment, symptom improvement and reduction in exacerbation of chronic bronchitis/COPD, associated with a reduction in hospitalisation rate and an improved quality of life.[42,44,45]

Data on the use of erdosteine in indications other than COPD are very scant. Nevertheless, 2 studies have shown beneficial effects of an erdosteine/amoxicillin combination in the treatment of paediatric patients with acute RTI.[46,47] Erdosteine alone, however, had no effects on paediatric patients with rhinosinusitis.[48]

The safety profile of erdosteine is generally quite good, the most common side effect being heartburn. No specific interactions with other drugs have been described.

Sobrerol

Sobrerol has been on the market of mainly European countries for almost 50 years. It has been shown in vivo to increase mucus production and ciliary motility, thus improving mucociliary clearance,[49] and to reduce the viscosity of tracheobronchial mucus without causing any alterations of the alveolar surfactants.[50] Radical scavenging activities have also been reported.[51]

Although recent, specific reviews exist for ambroxol,[15] bromhexine,[23] NAC and carbocysteine,[38,52,53] and erdosteine,[44,45,54,55] sobrerol has not received much attention, probably because most studies have been published in Italian and often in difficult-to-access journals. Only 1 old, outdated review on sobrerol has so far been published.[49] For this reason, we have decided to compile a tabular presentation of all available studies conducted with this compound (Table 1). A total of 10 double-blind and 15 open (controlled and non-controlled) studies conducted on adults and children have been published, covering acute and chronic airways diseases.[56,58–70,72–80,82,83] Sobrerol has been shown to be safe and effective also in paediatric patients and infants.[56,66–68,77,80,83] One study conducted on paediatric patients with whooping cough[83] suggests a synergistic effect of sobrerol with antibiotics similar to that observed for other mucolytics; no negative interactions were observed.[63,77,78]

In 2 studies, concomitant administration of sobrerol and paracetamol led to a better febrifuge action than the use of paracetamol alone.[57,81]

No clinical study reported any noteworthy AEs for sobrerol; the most common AEs reported (gastrointestinal problems and allergic reactions) were mostly of mild nature.

Discussion and Conclusions

Observational studies and real-life use have shown that mucolytics have an important place in the relief of upper respiratory tract symptoms by easing the elimination of mucus, even though the published literature regarding their effectiveness has been defined as inconsistent.[84] All drugs reviewed have shown comparable efficacy in the symptomatic treatment of productive cough, with some shared characteristics and some more specific features (Table 2).

Current guidelines and reviews of non-bacterial RTI recommend symptomatic cough relief treatment only.[85–87] The primary goal of treatment in case of productive cough is to support expectoration and thereby to indirectly reduce cough. To improve the patient's general condition, the treatment should also aim at a rapid recovery from symptoms secondary to cough such as sleep disturbance, impaired well-being, dyspnoea, and chest pain.[87]

All mucolytics reviewed here provide symptomatic cough relief and possibly shorten the duration of symptoms. They are also endowed with additional pharmacologic properties that may well contribute to their clinical benefit in the treatment of respiratory diseases such as bronchitis and COPD. The conflicting clinical evidence mentioned in recent reviews[11–14,33,88] is probably the consequence of several factors, such as the study designs used, the self-limiting nature of the disease, as well as the lack of well-defined study standards. There is also no clear consensus on end points to be used in clinical efficacy trials with mucolytics; for instance, the correlations between some efficacy end points are very poor, the acute or long-term effects of mucoactive therapy cannot be measured reliably, and the intra- and interpatient variability can be very high.[84]

The galenic form may also influence the effectiveness of a mucolytic drug but only little comparative evidence has been gathered with this drug class. One trial featuring a well-designed head-to-head comparison has studied nebulised products containing ambroxol, NAC, or sobrerol and has shown substantial differences among the 3 apparently identical galenic forms, with the sobrerol concentration in the aerosolised form being larger than that of ambroxol or NAC.[89] This may suggest, for instance, that a shorter sobrerol nebulisation could achieve the same results obtained with a longer nebulisation with ambroxol or NAC.

Table 1. Synopsis of clinical studies conducted with sobrerol.

INDICATION/ REFERENCE	STUDY DESIGN	MAIN END POINTS	DOSAGE/COMPARATOR/DURATION OF TREATMENT	SUBJECTS (SOB/ COMPARATOR) AGE	OUTCOME
Double-blind studies					
Acute airways diseases[56]	Double-blind, randomised, controlled	Cough, dyspnoea, rheological examination of expectorates, laboratory parameters	SOB granules 100 mg orally 3 times daily NAC granules 100 mg orally 3 times daily 7 d	40 (paediatric; 20/20) 3-12 y	Both treatments were effective and comparable. SOB was statistically significantly more active than NAC on the rheological values of sputum No serious AEs were reported for any treatment
Antipyretic activity in patients with RTI[57]	Double-blind, randomised, controlled	Clinical signs, fever	Combination tablets (paracetamol 300 mg and SOB 150 mg) orally 2 to 4 times daily or suppositories (500 and 200 mg) twice daily Paracetamol tablets alone, orally (500 mg 3-4 times daily) or suppositories (1000 mg 2-3 times daily) 5 d	287 (148/139) Age not clearly defined, mostly between 20 and 59 y	Efficacy of combination superior to paracetamol alone regarding cough and expectoration; faster resolution of fever with combination No serious AEs observed
Chronic and acute bronchitis[58]	Double-blind, comparative	Mucolytic activity	SOB orally Domiodol orally		Improvement in the subjective measures of ease of expectoration, severity of coughing, and sputum consistency No AEs reported
Chronic bronchitis[59,60,61]	Double-blind, randomised, crossover	Subjective symptoms, pulmonary function parameters, sputum characteristics	SOB 100 mg orally 4 times daily Placebo 14 d with 1 wk washout	30 (23 concluding the study) 64.5 y	No effects of SOB as an expectorant. Seven patients in the placebo dropped out of study No serious AEs observed SOB 2 patients with mild AEs. Placebo 6 patients with mild AEs
Chronic bronchitis[62]	Double-blind, randomised, controlled	Pulmonary function parameters, alveolar-arterial O_2 and CO_2 gradients	SOB 800 mg orally daily Placebo 7 d	20 (10/10)	Reduction in bronchial obstruction after SOB treatment Not significant modification of pulmonary functions
Chronic bronchitis[63]	Double-blind, randomised, placebo-controlled	Frequency of exacerbations and respiratory function indices	SOB 300 mg orally twice daily Placebo 3 mo	707, 673 completers (334/339) Mean age: SOB 55.6, placebo 57.5 y	No exacerbations in 76% patients of the SOB group as compared with 58% in the placebo group. Response of respiratory function indices significantly higher in the SOB group No serious AEs reported. SOB: 53 patients with side effects. Placebo: 66 pts with side effects
Chronic catarrhal rhinosinusitis[64]	Double-blind, randomised, placebo-controlled	Frontal headache and rhinorrhoea	SOB granules, orally, 900 mg/d Placebo Up to 10 d	40 (20/20) Mean age: SOB 40.6, placebo 43.9 y	Significant reduction in frontal headache and rhinorrhoea No serious or severe AEs reported
COPD[65]	Double-blind, placebo-controlled	Rheological mucus parameters	Combination (carbocysteine 375 mg + SOB 260 mg) orally (daily dose not specified) Placebo 10 d	32 (16/16)	Combination affected favourably the most important rheological parameters of mucus, including spinnability. Improvement of the most important respiratory function indices No AEs reported
Upper and lower acute or chronic RTIs[66]	Double-blind, randomised, controlled	Rheological mucus parameters, respiratory function indices	Combination (carbocysteine 375 mg + SOB 260 mg) orally 4 times daily Placebo Syrup: 21 d Capsules: 14 d	100 (50/50) 12 to 74 y	Significant improvement of objective and subjective symptoms and respiratory function indices as compared with placebo No AEs observed

Table 1. (Continued)

INDICATION/ REFERENCE	STUDY DESIGN	MAIN END POINTS	DOSAGE/COMPARATOR/DURATION OF TREATMENT	SUBJECTS (SOB/ COMPARATOR) AGE	OUTCOME
Whooping cough[67]	Double-blind, randomised, controlled	Clinical signs, respiratory function indices	Combination (clofedanol 1.62 mg/kg/d + SOB 3.6 mg/kg/d) Placebo 15 d	30 (paediatric; 15/15) 10 mo to 12 y	Rapid symptoms and respiratory function parameters improvement (in 60% for cough in SOB, 20% in PL) No AEs observed
Open studies (controlled and non-controlled)					
Acute, asthmatic, and recurrent bronchitis[68]	Open, randomised, parallel group	Improvement rates	SOB 50 to 100 mg orally twice daily BRH 2 to 4 mg orally 3 times daily 2 wk	40 (paediatric) <5 y	Both treatments effective, with similar improvement rates (SOB: 90%; BRH: 80%) No serious AEs reported. SOB: 2 patients with mild AEs. BRH: 3 patients with mild AEs
Acute, chronic and recurrent bronchitis, infectious bronchitis, pneumonia, bronchiectasis[69]	Open, observational	Mucus viscosity and symptoms improvement	SOB intramuscular twice daily, 120 mg daily 5 to 45 d	55 (34 F, 21 M) 15 to 87 y	Mucus viscosity reduced and symptoms improved No AEs reported
Bronchitis, bronchiectasis[70,71]	Open, case series	Cough, expectoration, dyspnoea	SOB suppositories (200 mg) and/or parenterally (60 mg) twice daily (60 cases) or nebuliser (2000 mg/100 mL H_2O) once daily or twice daily (30 cases) 3 to 6 d	90 Age not defined	Improvement of symptoms in most cases. Reduction in dyspnoea, eased expectoration. Improvements less pronounced with nebuliser No reports of AEs
Chronic bronchitis and emphysema[72]	Open, comparative (no treatment as control)	Respiratory function indices, rheological mucus parameters	SOB (nebuliser) SOB intramuscular 15 d	84 (50 nebuliser, 12 intramuscular, 22 no treatment) 43-69 y	Improvement of respiratory indices, decrease in mucus after 4-5 d, modification of rheological parameters No AEs reported
Chronic bronchitis[73]	Open, comparative, observational	Clinical signs, respiratory function parameters	Aerosolised SOB 80 mg/d and theophylline 600 mg/d orally Theophylline 600 mg/d orally 15 d	20 (10/10) 44 to 70 y	Mucus viscosity and respiratory function parameters better in the combination group. No severe AEs observed
Chronic bronchitis[74]	Single-blind, comparative	Mucus rheology and expectorate characteristics, cough	Combination (carbocysteine 375 mg + SOB 60 mg) orally 3 times daily SOB 100 mg orally 3 times daily 10 d	36 37 to 73 (mean: 60) y	Faster improvement of expectorate, clinical symptoms and respiratory functions with combination, no differences between the 2 treatments in mucus rheology and general outcome No AEs observed
Chronic bronchitis[75]	Open, comparative (no treatment as control)	Frequency of exacerbations	Combination (carbocysteine 375 mg + SOB 160 mg orally 3 times daily 6 mo	167 (116/51) Mean age: treated 60.3, control 62.1 y	Significantly lower number of exacerbation episodes in the treated group. Significant positive changes of the rheology of bronchial secretion No AEs reported
Chronic obstructive bronchitis[76]	Open, observational, multicentre	Clinical parameters, respiratory function indices	Combination (carbocysteine 375 mg + SOB 60 mg) orally 3 times daily 10 d	348 Median age: 61.6 y	Improvement of cough symptoms, expectoration, and dyspnoea as well as of respiratory function indices No severe or serious AEs observed
Chronic upper RTI[77]	Open, retrospective, comparative	Severity, frequency and duration of productive cough	Comparison between treatment with antibiotics vs treatment with mucolytic drugs (SOB or NAC)	59 (paediatric) (29/15/15) 3-14 (mean: 9) y	Antimicrobial therapy did not modify resolution of cough. Symptomatic therapy improved cough during treatment

(Continued)

Table 1. (Continued)

INDICATION/ REFERENCE	STUDY DESIGN	MAIN END POINTS	DOSAGE/COMPARATOR/DURATION OF TREATMENT	SUBJECTS (SOB/ COMPARATOR) AGE	OUTCOME
Chronic upper RTI[78]	Open, observational, prospective	Severity, frequency and duration of productive cough (patient diaries)	SOB orally Antibiotic therapy + SOB orally Antibiotic therapy only 28 d	150 (50/50/50) (144 completers) Mean age: 48 y	Treatment with mucolytics improved subjective symptoms better than with antibiotics alone, with no difference between SOB alone and SOB + antibiotics. A positive effect of SOB in cough reduction and resolution was observed No serious AEs were reported
Obstructive airways diseases[79]	Open, randomised, controlled	Sputum characteristics and volume, difficulty in expectorating, cough	SOB orally (granulate) Neltenexine orally (granulate) 20 d	30 (15/15) Mean age: SOB 70.2, neltenexine 65.1 y 29 to 82 y	Both drugs had similar efficacy, with no statistically significant differences in all measured parameters at end of treatment No AEs reported for neltenexine. SOB: 2 patients with AEs of moderate severity
Otitis media[80]	Open, observational	Nasal obstruction, earache, and deafness	SOB once daily, 40 mg/3 mL daily 10 d	30 (paediatric) 5 to 10 y	Significant reduction in nasal obstruction, earache and deafness No serious AEs reported. Two patients with probably related moderate asthma attack, resolved with 50% dose reduction
Safety, antipyretic activity[81]	Open, observational, multicentre	Clinical parameters	Paracetamol and SOB suppositories (56%) or orally (44%) (dosage not available) 1 to 2 d: 5%, 3 to 4 d: 69%, >4 d: 26%	3501 (1916 treated with the paracetamol-SOB association) Age not clearly defined	Paracetamol-SOB combination was more effective than other treatments in reducing fever No serious AEs observed. Incidence of AEs in the paracetamol-SOB group significantly lower than in other treatment groups
Upper and lower acute or chronic RTIs[82]	Open, observational	Rheological mucus parameters, respiratory function indices	Combination (carbocysteine 375 mg + SOB 60 mg) orally 4 times daily 14 d	50 20 to 70 (mean: 42) y	Improvement of sputum fluidity and favourable evolution of respiratory function parameters No AEs observed
Whooping cough[83]	Open, observational	Time course to symptom resolution	SOB orally or suppositories Salbutamol 0.30 to 0.50 mg/kg/d, orally, 4 times daily Erythromycin 40 mg/kg/d, orally 3 times daily Treatment: until resolution of symptoms (erythromycin 6-8 d)	20 (paediatric) 6 mo to 2 y	Treatment outcome was superior to historic controls (use of antibiotic alone or associated with hyperimmune gamma globulins and/or sedatives) No AEs reported

Abbreviations: AE, adverse event; BRH, bromhexine; NAC: *N*-acetyl cysteine; SOB, sobrerol.

Table 2. Main features of the mucolytic drugs reviewed.

	AMBROXOL	BROMHEXINE	CARBOCYSTEINE	*N*-ACETYL CYSTEINE	ERDOSTEINE	SOBREROL
Indications covered by studies	BE, BR, CF, COPD, (IRDS)[a], RTI	BE, BR, CF, COPD, (IRDS)[a], RTI	BR, COPD, RTI	BR, COPD, RTI	BR, COPD, RTI	BE, BR, CF, COPD, O, R, RTI, W
Safety[b]	Allergic skin reactions	Allergic skin reactions	Paradoxical AEs in paediatric patients	Paradoxical AEs in paediatric patients	n.k.	n.k.
Paediatric use[c]	NR2	NR2	NR2	NR2	NR2	NR2
Interactions/synergies						
Antibiotics	Increases levels	Increases levels	n.k.	n.k.	n.k.	Increases levels
Antipyretics (paracetamol)	n.k.	n.k.	n.k.	n.k.		Increases efficacy
Other	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.

Abbreviations: BE, bronchiectasis; BR, bronchitis; C, common cold; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IRDS, infant respiratory distress syndrome; O, otitis media; R, rhinosinusitis; RTIs, respiratory tract infections (not specified); W, whooping cough. Galenic forms: A, ampoules; Ca, capsules, pastilles, lozenges; Gr, granulate; Ne, nebuliser; Su, suppositories; Sy, syrup. n.k., not known or not reported. NR2: not recommended in children <2 years old.
References are listed in the corresponding sections.
[a]No longer first-line treatment option.
[b]Only major safety issues.
[c]Use in infants in some countries allowed.

Positive interactions with antibiotics have been reported for ambroxol,[17–20] bromhexine,[24–26] and sobrerol.[83] In the context of the indications for which mucolytics are used, however, this property is of limited usefulness.

However, 2 studies report a positive interaction of sobrerol with an antipyretic.[57,81] This synergistic effect should be further investigated. Paracetamol is often used by patients with common cold symptoms to reduce fever, and if the concomitant treatment of both drugs leads to a better antipyretic action of paracetamol than administration of paracetamol alone, the paracetamol dosage could be decreased without loss of efficacy and possibly with a reduction in potential AEs.[57]

All mucolytics discussed in this review have a good safety profile, although some precautions should be taken when using ambroxol and bromhexine[21] and the use of NAC and carbocysteine should be monitored in special patient groups.[21,39–41]

Ambroxol, bromhexine, carbocysteine, erdosteine, NAC, and sobrerol may alter the volume of secretions or their composition; therefore, they can effectively ease symptoms of respiratory tract diseases such as productive cough. Their mucolytic, anti-inflammatory, and antioxidant properties all contribute to their clinical benefit. In patients with COPD, they may help to reduce frequency and duration of exacerbations. Upper RTIs being a multifaceted disease, treatment must rely on the simultaneous treatment of all symptoms. In addition, the overall treatment success is dependent on a number of additional factors. For instance, in indications such as COPD or chronic bronchitis, adherence to treatment and simultaneous targeting of different pathological mechanisms are crucial to achieve symptoms resolution. Overall, the available evidence from randomised, controlled, and observational trials, as well as pragmatic, real-life experience, suggest that these mucolytics, taken at the recommended dosages, are useful in the therapy of lower respiratory diseases such as COPD and bronchiectasis, as well as of upper respiratory airways infections, including bronchitis, sinusitis, and rhinosinusitis.

Author Contributions

Both authors contributed equally to the design, preparation and writing of this review.

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