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Carbocysteine as Adjuvant Therapy in Acute Respiratory Tract Infections in Patients without Underlying Chronic Conditions: Systematic Review and Meta-Analysis

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Abstract

Objective: This study aims to systematically examine the existing evidence regarding the clinical benefits of carbocysteine as an adjunctive treatment in acute bronchopulmonary and otorhinological processes. **Design**: Systematic review and meta-analysis. **Data sources**: An electronic search was conducted across PubMed, Cochrane Library, clinicaltrials.gov, and the European Clinical Trial Register, with the search dated to May 2023. Bibliographic references from other literature reviews and meta-analyses were also reviewed. The search was limited to randomized clinical trials published in any language and year. It was completed by cross-checking the references of the located articles. **Methods**: Inclusion criteria covered studies assessing systemic or inhaled carbocysteine, regardless of dosing regimen. Concomitant medication use was acceptable if balanced between intervention and control groups. Authors independently extracted data, resolving disagreements through consensus. Methodological quality assessment relied on critical reading of each study. Dichotomous variables were analyzed using odds ratio (OR), and a final effect size was calculated. Statistical significance was established when confidence intervals did not cross the neutral value. Heterogeneity was assessed via the X^2 test and I^2 index. **Results**: Out of 318 initially identified studies, 4 met inclusion criteria. The meta-analysis for poor general condition yielded an OR of 0.45 in favor of intervention, p = 0.013, with non-significant heterogeneity. Cough events showed a percentage of 15.8% for carbocysteine

vs. 27.2% for placebo. On the seventh day, expectoration rates were 18.37% for carbocysteinevs 33.3% for placebo. **Conclusions**: The observed clinical benefits align with carbocysteine's mucoactive and muco-regulatory properties, complemented by anti-inflammatory and antioxidant actions. Carbocysteine stands out among mucolytic agents. In the context of persistent infectious diseases, the study emphasizes the need for further exploration of carbocysteine's therapeutic potential as an adjunctive treatment for acute respiratory infections. These findings underscore its significance in the evolving landscape of respiratory healthcare.

Keywords

Acute Respiratory Infections, Carbocystenine, Systematic Review, Meta-Analysis

1. Introduction

Acute respiratory infections (ARIs) rank as the second most prevalent cause of morbidity and mortality globally, accounting for approximately 4.25 million deaths annually [1]. These infections can originate from variety of pathogens, including viruses, bacteria, and fungi [2]. Viral ARIs represent the predominant category of these illnesses and frequently lay the groundwork for subsequent bacterial infections, with tend to manifest with heightened severity in clinical outcomes. Streptococcus pheumoniae and Haemophilus influenzae are among the primary bacterial culprits known to cause ARIs [3].

These infections severely impact the quality of life in individuals with preexisting respiratory issues. Notably, 37% of adults hospitalized for acute asthma show signs of recent respiratory tract infections, primarily due to influenza A and rhinovirus [4]. This highlights a significant burden on healthcare systems, both in terms of economic impact and resource strain [5]. For instance, the increasing number of patients recuperating from COVID-19 encounter various health complications, necessitating extended healthcare support and resource allocation [6]. Furthermore, hospitals must brace for potential surges in cases resulting from emerging infectious diseases like respiratory pathogens [7]. This preparation demands significant investment in resources, including space, staffing, equipment, and system management, underscoring the substantial strain placed on healthcare infrastructure [8].

Among the specific interventions for these pathologies, mucolytics help to reduce the viscosity of mucus in the lungs and airways. By reducing mucus density, productive coughing is facilitated, allowing mucus to be expelled more easily [9]. In this context, carbocysteine is a mucoactive drug. It has been available in the European Union for over 50 years and has extensive clinical experience. It is used as a mucolytic and mucoregulator in bronchopulmonary and otorhinological processes. These processes include conditions like rhinopharyngitis, rhino-

sinusitis, seromucous otitis, and acute bronchitis. These conditions often involve altered mucociliary clearance due to excessive mucosal secretion and changes in mucus viscosity and elasticity. These changes lead to mucus accumulation and bacterial overgrowth, making it difficult to clear.

Carbocysteine's significance has risen notably during the SARS-CoV-2 pandemic, largely due to the infection's tendency to provoke excessive mucus production, thicken mucus, and trigger substantial inflammation. Its mechanism of action, which disrupts the ciliary movement in the upper airways—the initial site of SARS-CoV-2 infection—enhances mucus clearance and may prevent the virus from progressing to the lower respiratory tract [10]. Additionally, carbocysteine's capacity to reduce the risk of secondary bacterial infections and alleviate oxidative stress is particularly beneficial in managing patients with chronic obstructive pulmonary disease (COPD). These characteristics position carbocysteine as a promising option for both post-exposure prophylaxis and the early treatment phase of COVID-19, especially when used alongside treatments such as monoclonal antibodies, antivirals, anti-inflammatory agents, and corticosteroids administered via inhalation [11].

This muco-regulator, derived from the amino acid L-cysteine, not only acts like other mucolytic drugs (N-acetylcysteine (NAC), erdosteine) by breaking the bonds of mucus glycoproteins, but also acts on the metabolism of mucus-secreting cells, as a true muco-regulatory drug, correcting alterations in glycoprotein synthesis (increasing the proportion of sialomucins at the expense of fucomucins), restoring mucus viscosity and elasticity, which facilitates mucociliary clearance and drainage of secretions [12] [13]. Carbocysteine supports glutathione synthesis, crucial for cellular redox balance, which indirectly aids in the proper synthesis and function of glycoproteins. This mechanism enhances cellular health by influencing the activity of enzymes involved in glycoprotein processing, highlighting its therapeutic importance in conditions characterized by oxidative stress and glycoprotein dysfunction [14].

Carbocisteine also allows antibiotics to penetrate more easily through this hematobronchial barrier [15]. Associated with its mucoactive properties, carbocysteine has been shown to have antiviral effects on human rhinovirus, respiratory syncytial virus, and influenza virus, all of which interfere with upper airway ciliary motility [16] [17].

Carbocysteine leads to more effective mucus clearance and possible containment of viral spread to the lower respiratory tract. Positive effects have been documented in terms of limiting superimposed bacterial infection and reducing oxidative stress as a free radical inactivator [18] [19] and anti-inflammatory actions by reducing cytokines in rhinovirus infections and the expression of mRNA coding for ICAM-1, a receptor for a broad group of rhinoviruses [20]. All these actions have determined that carbocysteine is considered an option in the treatment of acute infectious processes of the upper and lower respiratory tract due to its muco-regulatory and mucoactive, anti-inflammatory and antioxidant properties.

The objective of this study is to review the available evidence on the clinical benefits of carbocysteine as an adjuvant treatment in acute bronchopulmonary and otorhinological processes.

2. Material and Methods

2.1. Search Strategy

We conducted an electronic search of PubMed, Cochrane Library, clinicaltrials.gov, and the European Clinical Trial Register, with the search dated to May 2023. Bibliographic references from other literature reviews and meta-analyses were also reviewed. The key search terms used were: "carbocysteine", "respiratory tract infection", "cough", "bronchitis", "bronchiolitis", "pneumonia", "laryngitis", "rhinitis", "influenza", "pharyngitis", "sinusitis". The search was limited to randomized clinical trials (RCTs) published in any language and year. It was completed by cross-checking the references of the located articles.

2.2. Study Selection

Study selection was performed independently by two of the review authors and any disagreement was resolved by consensus. Only studies with RCT design that met the following established inclusion criteria were selected. Subjects of any age, with systemic or inhaled carbocysteine intervention for acute respiratory tract pathology with or without hearing impairment compared to a placebo group. Observational studies, before-after and uncontrolled trials were excluded. We also excluded studies involving subjects with underlying chronic conditions, such as cystic fibrosis, chronic obstructive pulmonary disease, or bronchopulmonary dysplasia.

The included studies were to evaluate the systemic or inhaled use of carbocysteine regardless of the dosing regimen. These studies could use concomitant medication to treat the pathological condition if this was done equally in both intervention and control groups.

The studies were required to evaluate at least one of the following: clinical resolution of symptoms or signs, measured in terms of frequency, percentage, or using a specific cut-off point; a global assessment of improvement by either the physician, patient, or their guardians; or the impact on the quality of life.

Data extraction from the included studies was carried out independently by all the authors of the review and possible disagreements were subsequently agreed upon. The methodological quality of the studies was assessed based on a critical reading of each of these studies. No specific tool was used to assess the quality of the studies due to the age of publication of the papers and, therefore, the heterogeneity found in the text structures of these articles.

The authors of the included papers were not contacted to request data or clarifications, as the publications were more than 20 years in age.

2.3. Statistical Planning

For the study of dichotomous variables, odds ratios (OR) were calculated indi-

vidually for each of the studies analyzed. Subsequently, a final estimator or effect size was generated from the inverse of the variance of each study. Statistical significance was considered when the confidence interval of the effect size did not cross the neutral value. Heterogeneity between studies was studied statistically using the χ^2 test and the I^2 index. Using a random effects model when the heterogeneity found was statistically significant $p < 0.05$. While when no statistical significance was found in the heterogeneity test, a fixed effects model was chosen. The analyses were presented in forest plot graphs, and the risk of publication bias could not be determined from funnel plot graphs for each outcome measure evaluated due to the small number of studies included in each comparison. All analyses were performed with the statistical program STATA SE 14.2 (metan).

3. Results

A search of the literature and references identified 318 potential studies, of which 118 were obtained and 50 of them assessed for eligibility. From these studies, after reading them, 4 were selected that met the inclusion criteria established in this review [21] [22] [23] [24]. The main reasons for the exclusion of studies were the medical condition, focused on chronic pathology, and the design of the studies with many observational studies or without a control group (**Figure 1**).

Regarding the included studies, two were written in Italian [21] [24], one in French [22] and one in Japanese [23]. The mean age of the studies was 39.25 years. The quality assessment of the included studies was carried out qualitatively due to the heterogeneity in the structure of the articles due to their age.

3.1. Included Studies

The Bonci-1994 study [21] was conducted in 40 children aged 6 to 7 years with secretory otitis media and 30 adult patients with acute inflammatory middle ear pathologies. The comparison group was placebo, and antibiotics and anti-inflammatories were prescribed in both arms for the acute pathology. The outcome measures observed were subjective symptoms such as hearing loss or fever in the pediatric study and healing in the adult study. Parameters were assessed every three days and up to a maximum of 15 days of therapy. The randomization process is not reported, although the double-blind study consideration is indicated. To cover the objective of this review, only the study in acute pathology was used.

The Malka-1990 [22] study is a multicenter trial in acute bronchitis with 13 general practitioners coordinated by a pulmonologist. The duration of the interventions was 7 days with doses between 200 and 300 mg/day in children aged 2 to 12 years. The randomization process and blinding of the interventions are not reported.

The Nakayama-1977 [23] study is a work published in Japanese that initiates two studies with single-blind design to determine doses and, subsequently,

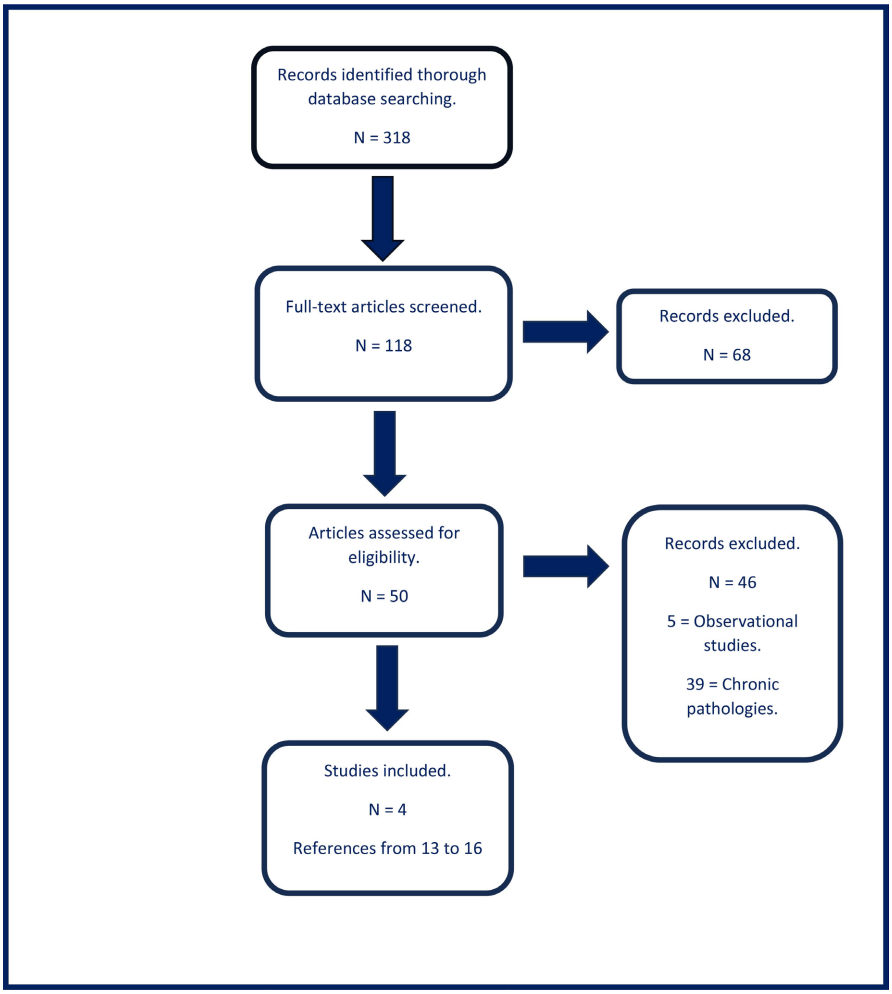

Figure 1. Flow diagram of systematic review methodology and process for studies inclusion.

a double-blind trial is performed for 7 days to check the efficacy of the dosage obtained in the previous studies. The participating subjects in this study encompass the age range from 0 to 18 years. No data are given about the randomization process, although it is indicated that the study was double-blinded and that this was verified by personnel outside the research. Also, the statistical analysis was performed by an independent professional. However, it is indicated that not all the subjects initially included in the study were analyzed.

The Zanini-1974 study [24] is a paper written in Italian with 30 children hospitalized for acute respiratory infection with carbocysteine intervention between 5 and 9 days depending on the age of the subjects and doses between 100 and 400 mg/day. Outcome measures assessed were cough, dyspnea, temperature, and general condition. It is indicated that the subjects were randomly assigned to the interventions, although details of the process followed are not given. The double-blind design did not preclude clinicians from noting that one of the interventions achieved better efficacy results than the other intervention arm. More details in **Table 1**.

Table 1. Characteristics of included studies.

Study	Methods	Subjects	Pathologies	Interventions	Outcomes
Bonci 1994	RCT Doble-blinding Placebo controlled	Adult patients < 16 years old.	Acute inflammatory pathologies of the middle ear.	Oral carbocysteine for a maximum of 15 days. 400 mg/day.	Subjective symptoms as hearing loss, overall assessment.
Malka 1990	RCT Doble-blinding Placebo controlled	Paediatric ambulatory 2 - 12 years.	Acute bronchitis.	Oral carbocysteine for 7 days. 200 mg/day and 300 mg/day in > 5 years old.	Cough, expectoration, dyspnoea.
Nakayama 1977	RCT Doble-blinding Placebo controlled	Paediatric ambulatory 0 - 18 years.	Acute bronchitis.	Oral carbocysteine 30 mg/kg/day for 7 days.	Overall assessment, stridor, expectoration, cough.
Zanini 1974	RCT Doble-blinding Placebo controlled	Paediatric hospitalization.	Acute respiratory infections.	Oral carbocysteine 100 to 400 mg/day for 5 to 9 days.	Cough, dyspnoea, temperature, general condition, appetite.

RCT: Randomized Clinical Trial.

3.2. Meta-Analysis

Due to the age of the publications, which affects the quantitative information extracted, only the outcome measures of dyspnea and poor general condition could be meta-analyzed. Likewise, the Zanini-1974 and Malka-1990 studies provide individual data.

3.2.1. Dyspnea

We have data from two studies that contribute a total of 136 patients to the joint analysis, showing an effect size of OR 0.86 in favor of the intervention but not reaching statistical significance, p = 0.781. The heterogeneity found was moderate with an I^2 of 38.2% (**Figure 2**).

3.2.2. Poor General Condition

For this outcome we have data from three studies that contribute a total of 112 subjects to the joint analysis, with an effect size of OR 0.45 in favor of the intervention and obtaining statistical significance, p = 0.013. The heterogeneity was not statistically significant (**Figure 3**).

3.3. Aggregate Data by Study

For aggregate data in each study, the Zanini-1974 study evaluates fever at six days, not observing any case between both intervention and control groups. Regarding the cough event, at six days this same study observed different percentages in the intervention and control groups with 15.8% for the carbocysteine arm vs. 27.2% for the placebo arm, p = 0.44. Also, in relation to appetite problems at the end of treatment, this same study shows that no cases were observed

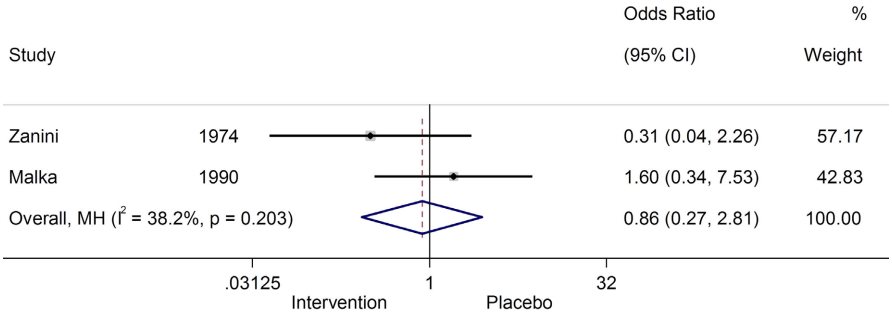

Figure 2. Outcome: Dyspnea. MH: Mantel-Haenszel; n: Subjects without the outcome; N: Subjects with the outcome. CI: Confidence interval; p-value; I^2: Index of heterogeneity.

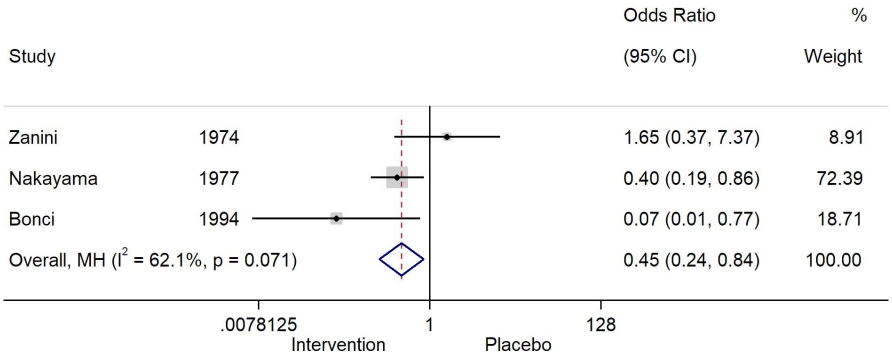

Figure 3. Outcome: Poor general condition. MH: Mantel-Haenszel; n: Subjects without the outcome; N: Subjects with the outcome. CI: Confidence interval; p-value; I^2: Index of heterogeneity.

in the carbocysteine group while this event did occur in one subject in the placebo group, representing 9% of the total subjects in that group, p = 0.18. The Malka-1990 study provides data on expectoration on the seventh day of treatment with percentages of 18.37% for the carbocysteine group vs. 33.3% for the placebo group, p = 0.081 showing a trend close to statistical significance.

4. Discussion

Carbocysteine is a muco-regulatory and mucoactive drug used as a symptomatic treatment in acute and chronic infectious airway pathology. This systematic review evaluated its efficacy for the treatment of acute upper and lower airway infections in pediatric and adult age without underlying chronic conditions. The studies included in this systematic review demonstrated a positive effect of the mucolytic carbocysteine in treating ARIs. However, due to limitations related to the quantity, quality, and age of the available studies, it is advisable to replicate the objectives in new studies to validate the observed results.

Only four clinical trials met the inclusion criteria according to the objectives of this review. Among these trials, three were conducted in the pediatric population, and one involved subjects aged 16 years and older with hearing impairment. Notably, when analyzing both subject profiles together for the outcome measure of general condition, there was no significant heterogeneity in the re-

sults. This analysis revealed a clear and favorable effect of carbocysteine. Consequently, the results appear to be consistent for this variable, suggesting that the effects in various age groups may be similar or at least not significantly different. Thus, this aspect further validates the findings, emphasizing the importance of current high-quality research designs with sufficient statistical power to conduct subgroup analysis that encompass age and the diverse effects brought about by acute pathology.

The age of the studies posed challenges in consolidating data for joint analysis; nonetheless, aggregated data from these included studies were accessible. For the assessment of the cough variable, there was a nearly twofold increase in incidence observed in the placebo group compared to the carbocysteine intervention at the conclusion of the study [24]. A similar trend was evident for the expectoration variable, with an almost twofold increase in incidence in the placebo goup [22]. In both cases, while the patterns are evident, statistical significance was not achieved, likely due to the limited sample size in these studies.

On the other hand, outcome measures that did not demonstrate significant effects for carbocysteine when compared to placebo included dyspnea, where data from the two meta-analyzed studies were inconclusive and heterogeneous, fewer, where the passage of time and concomitant medication seemed to affect both groups similarity, thus balancing the results, and issues related to appetite, with were only reported in a single case in the placebo group of the study.

Mucolytics are commonly prescribed by pediatricians and family physicians to manage acute upper and lower respiratory tract infections in both pediatric and adult patients [25]. These mucolytic agents serve as adjunctive treatments in conditions characterized by excessive secretion and heightened mucus viscosity, with can impede proper mucociliary drainage. Various mechanisms disrupt ion transport pathways responsible for mucus hydration, promoting the formation of mucus accumulations that create a conductive environment for obstruction, inflammation, and superinfection [26].

Carbocysteinehas been associated with benefits in treating upper and lower respiratory tract infections for decades due to its mucolytic, muco-regulatory, and mucoactive properties. Additionally, carbocysteine exhibits a wide range of anti-inflammatory and antioxidant activities, both in vitro and in vivo. These attributes have been demonstrated in animal models and human studies, indicating its ability to reduce cytokine-driven inflammation in viral infections, prevent bacterial adhesion to epithelial cells [17] [18], and enhance the penetration of antibiotics through the blood-bronchial barrier [15].

Furthermore, there has been growing interest in the potential role of mucolytics in the treatment of SARS-CoV-2 infection in recent years [27] [28]. It's worth nothing that carbocysteine has demonstrated antiviral effects against human rhinovirus, respiratory syncytial virus (RSV), and influenza virus. Additionally, it has been found to influence ciliary motility in the upper airways, which is the primary site of SARS-CoV-2 infection. This influence on ciliary motility in the upper airway is a key aspect of its antiviral action. Cilia in the respiratory tract

play a critical role in the body's defense against respiratory viruses by moving mucus, which traps pathogens, out of the respiratory tract. When respiratory viruses infect the upper airway, they often disrupt normal ciliary function, hindering this natural defense mechanism. Carbocysteine, as a mucolytic agent, helps in restoring ciliary efficiency by modifying the rheological properties of mucus, making it less viscous and easier to clear [10]. This enhancement of ciliary function leads to more effective mucus clearance, crucial for eliminating trapped viruses and other pathogens from the respiratory tract. Consequently, carbocysteine's effect on mucus clearance may help limit the viral spread to the lower airways [10].

Thus, the pharmacological properties of carbocysteine make it an ideal candidate for supportive treatment in viral infectious processes of the upper and lower respiratory tract with abundant secretion and difficulty in adequate mucociliary drainage.

In conclusion, the study provides a comprehensive examination of carbocysteine's role as an adjunctive treatment in ARIs. It highlights carbocysteine's mucoactive, muco-regulatory, anti-inflammatory, and antioxidant properties, reinforcing its efficacy in treating acute bronchopulmonary and otorhinological processes. The findings indicate its broader impact in managing respiratory infections, emphasizing the need for further research into its therapeutic potential. This research contributes to a deeper understanding of carbocysteine's multifaceted benefits, especially in the context of ARIs without underlying chronic conditions. The study underscores the importance of continuing exploration into carbocysteine's pharmacokinetics and dynamics, aiming to bolster its application in respiratory healthcare.

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IRB approval status: Not applicable.

Clinicaltrials.gov (or Equivalent) Listing (If Applicable)

Not applicable.

Conflicts of Interest

MCR has received speaker fees from AstraZeneca, Bial, Chiesi, CSL Behring, GSK, Menarini, and Grifols, and consulting fees from GSK, Bial, and ITF Research Pharma. SB has received speaker fees from GSK, AstraZeneca, and ITF Research Pharma. JLRM has done consulting or training work for Abbvie, Takeda, Abbott, ITF Research Pharma, Janssen, Rovi, Rubio, GSK, Lilly, Servier and MSD. MRC is a full-time employee at ITF Research Pharma S.L.U.

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