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Can Big Data Analyses Help Speed Up the Clinical Development of Mucoactive Drugs for Symptomatic RTIs?

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Abstract This paper highlights the need for validated models to demonstrate mucoactive drug efficacy in relieving respiratory tract infection (RTI) symptoms and suggests new concepts to further ongoing research. The review is based on the analyses of studies published on mucoactive drug in respiratory diseases, data supporting FDA's expectorant monograph, and related US consumer use and attitude surveys. The changes in the volume and consistency of respiratory mucus during RTIs may result in ciliary dysfunction, mucus accumulation, and symptoms like cough and chest congestion. Mucoactive drugs can provide relief, but limited choices exist in the US, due to the unavailability of validated clinical models and unequivocal efficacy results. Ongoing developments have not provided definitive solutions, and Big Data analysis techniques may help overcome current clinical research limitations by identifying differentiating disease and patient factors to speed up the development process to substantiate the effectiveness of expectorant/mucoactive drugs in relieving RTI symptoms.

Keywords Mucus · Cough · Mucoactive drugs · Guaifenesin · Effectiveness · Big Data

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Introduction

Airway mucus is essential for the functioning and viability of the respiratory tract.

It serves as a physical barrier; humidifies and warms the inhaled air; may buffer inhaled, potentially toxic gases; exerts antimicrobial activity; and is part of the innate respiratory tract immune defense system [1]. To maintain optimal functionality, secreted mucus must continuously display proper viscoelasticity for effective mucociliary clearance (MCC).

Normally, the MCC process is effective in removing mucus and foreign particles trapped from inhaled air. Airway infections and inflammation modify the production of certain mucins, the polysaccharide components that determine mucus consistency and rheology, impairing mucus functionality in maintaining healthy airways [1]. If physiological functions, such as optimal mucus rheology and effective MCC, fail to clear mucus from the airways, the body will trigger coughing, as a natural defense to keep the lungs clear.

Acute and chronic respiratory disorders, such as RTIs or chronic bronchitis (CB), are often associated with mucus hypersecretion [1–3]; impede overall health, productivity, and well-being; and pose significant public health burdens worldwide [4].

Studies among sufferers from acute RTIs identified frequently experienced symptoms, including chest congestion, cough, sore throat, blocked and runny nose, postnasal drip, sneezing. [5–7]. Symptom relief, to help RTI sufferers maintain daily activities and achieve good-quality sleep as the infection resolves, is a significant driver for therapy, typically with over-the-counter (OTC) cough and cold medicines. For symptoms associated with excess respiratory mucus production, mucoactive/expectorant treatments are favored [8].

Table 1 Different types of mucoactive drugs

Mucoactive drugs	Proposed MOA
Expectorants	Increase mucus hydration to volumes more easily expectorated by coughing (e.g., guaifenesin)
Mucokinetics	Increase mucus transportability by cough (e.g., ambroxol)
Mucolytics	Reduce mucus viscosity by cleaving mucin disulfide bonds (e.g., N-acetylcysteine)
Mucoregulators	Reduce mucus hypersecretion (anticholinergics)

Currently, there are about 50 compounds claimed to have beneficial effects on respiratory tract mucus [3, 9, 10]. These "mucoactive" drugs [3] can be classified into four categories (see Table 1), according to their putative mechanism of action (MOA).

While multiple mucoactive drugs are available around the world, only two compounds are available in the US for the relief of cough and chest congestion due to RTIs and CB:

1) Guaifenesin, an expectorant, available OTC in different formats (e.g., immediate-release liquids, granules, and tablets; extended-release tablets).
2) N-acetylcysteine, a mucolytic agent, available only as nebulizer solution (Rx only).

Why are there so few FDA-approved mucoactive products available in the US?

Methods

Relevant published clinical studies about mucoactive drugs in respiratory diseases were reviewed, together with clinical data supporting the OTC monograph for expectorants [11] and specific consumer use and attitude surveys regarding expectorants.

Results

Published studies of mucoactive drugs in individuals suffering from the common cold show significant heterogeneity of patient populations and methodology, with different inclusion criteria, dosage regimens, treatment durations, subjective assessment methods, and reporting results. Informative meta-analyses of these data are essentially not available as published studies with different mucoactive compounds in RTI patients (e.g., guaifenesin) have not been considered suitable for sound and robust data pooling. On the other hand, there are good examples for successful meta-analyses that have been conducted to assess the effectiveness of mucoactive drugs, such as N-acetyl cysteine or erdosteine, in alleviating the symptoms of CB [12] or reducing the frequency of acute exacerbations in CB or COPD patients [13, 14]. This contrast in the robustness of studies with mucoactive drugs in CB versus RTI patients highlights the need for better clinical methods in the testing of cough and cold treatments. Nevertheless, in the absence of solid randomized, controlled trials (RCTs), meta-analyses, if done with proper attention to the quality and nature of the individual trials, may be a worthwhile exercise that could provide certain indirect treatment comparisons of the available clinical evidence and yield key insights by exploring sources of heterogeneity, stratified analyses, and meta-regressions [15].

Over the past several decades, there has been limited investment in developing improved methods and new products for the treatment of the common cold. These factors and FDA's current requirements for approval of these products suggest that the limited choice of mucoactive drugs available in the US is due to the lack of validated assessment tools to demonstrate the effectiveness of mucoactive drugs for the relief of RTI symptoms [2, 3, 16]. The safety of these products is generally well documented (e.g., post-marketing pharmacovigilance) and not a major concern [10].

Regulatory approval of mucoactive products for the relief of RTI symptoms in different countries was largely based on studies in CB patients [17, 18]. Although some studies showed satisfactory evidence of efficacy and safety, they employed various subjective clinical methods to show improvements in cough (severity and frequency), mucus expectoration or symptoms of chest congestion in CB patients [17, 19]. Methods were not validated or were not confirmed in subsequent studies [10]. Some studies used objective endpoints, including demonstration of the MOA (MCC) or the reduction of acute exacerbations of CB [12, 20–22].

In the US, guaifenesin was included in the FDA's OTC monograph based on several CB studies, establishing the drug as safe and effective [11]. There are some published RCTs providing support for the effectiveness of guaifenesin also in relieving RTI symptoms. Using different clinical models, they assessed parameters such as cough frequency and intensity and chest discomfort associated with cough [23] or a reduction in cough reflex sensitivity [24]. In fact, the latter method is validated, but this surrogate endpoint is not recognized as substantiating efficacy by regulatory agencies. Nevertheless, the above-mentioned absence of widely accepted, validated endpoints remains

the central issue impeding further development of expectorants/mucoactive drugs.

Despite these scientific and regulatory concerns, expectorants are widely used in the US by RTI sufferers and recommended by doctors, suggesting that these products provide satisfactory symptom relief and tangible benefits (real-world evidence), but clinical model(s) to demonstrate these effects remain elusive.

There is ongoing research to develop patient-reported outcome (PRO) tools for expectorants and cough/cold products in adults and children. Pediatric programs are conducting naturalistic (non-interventional) studies [25], to understand how children experience onset and natural resolution of their RTI symptoms, which inform the development of psychometrically validated child-appropriate PRO tools.

PRO parameters for adults have been tested in a clinical pilot study. A randomized, double-blind, placebo-controlled, exploratory study evaluated extended-release guaifenesin using several objective and subjective assessment tools in RTI patients ($n = 378$) to identify promising leads, which could then be refined and tested in post hoc analyses [26]. Patient mucus samples were analyzed as objective endpoints, but due to sample-related and other methodological issues, this was not a proactive outcome variable [27]. A patient-completed 11-question daily diary showed several questions with positive outcomes compared to the placebo group (statistically significant or strong trends). Focus on questions most relevant to patients yielded more robust and significant efficacy results (SUM8, $p = 0.037$) in post hoc analyses and led to the development of a validated 8-Question patient-reported outcome (PRO) tool for use in future studies [26].

The exploration and refinement of PROs in clinical studies is expensive, time consuming, and may produce patient-reported outcomes that do not reflect the relevant OTC (real world) drug treatment experience. Another source for new approaches and insights into studying the effectiveness of mucoactive treatments could be the field of comparative effectiveness research (CER), which uses pragmatic clinical studies for direct comparison of existing health care interventions to determine which treatment works best, for whom, and under what circumstances, thus providing potential guidance for decisions about how to best tailor treatments for certain subsets of patients [28, 29].

The above referenced clinical methods and research strategies are important, but there is also a need for a more efficient process to identify critical symptom and patient factors and pre-evaluate them before they are assessed in costly clinical trials.

Survey results in cough and cold sufferers [7] suggest that consumers may be capable of effectively differentiating effects of expectorants in improving their mucus-related RTI symptoms without using traditional clinical research methods. The data indicate that two different groups of consumers, who individually took 1 of 2 different products but with the same active expectorant and dosage regimen, rated the two products very similar. The two groups were tested independently, and the comparative experiment might be viewed as randomized and blinded, although the survey was not formally set up that way.

This finding suggests that, if sufferers of RTI symptoms can fairly accurately self-assess the product performance of an expectorant in a ('blinded') survey setting, there may be ways to more effectively utilize consumer surveys and related instruments (incl. social media) to quantitate the performance factors of OTC medicines.

A radically different approach to bolster the evaluation of difficult-to-assess treatments for short-term, transient OTC conditions could be the utilization of Big Data analysis techniques—including dynamic processing, modeling, and analytics—to explore the respective technology, consumer, and marketplace data landscapes. Such algorithms may be able to extract hitherto in-accessible consumer experiences related to the use of OTC drugs (like guaifenesin) and could serve to inform patient selection factors and clinical study designs. Big Data analyses may become a key factor in accelerating drug development and regulatory approval timelines.

Discussion

Mucoactive drugs (guaifenesin in the US) are potentially useful in providing relief from nagging, mucus-related RTI symptoms, such as cough or chest congestion, but currently we are lacking reproducible assessment instruments in RCTs to confirm their efficacy in patients suffering from the common cold.

RCTs are complex and expensive testing systems for the evaluation of nuanced clinical models and parameters. This is especially true for RTI studies, due to the self-resolving illness and variability of patient and symptom factors. Other research tools, such as meta-analyses of available clinical evidence or the use of pragmatic trials, offer alternatives but are also not suitable for fast, inexpensive and unencumbered exploration of new concepts.

Assuming that mucoactive drugs can be shown to be effective with the appropriate clinical approach (as has been done in CB and COPD patients), an economical system to evaluate multiple variables and factors, before testing the best selection in an RCT, is likely to save time and resources. Big Data analysis techniques may deliver this promise and prove effective in pre-qualifying differentiating disease and patient factors.

Until recently, this approach was not feasible. Established digital libraries (e.g., PubMed) encompass only

certain types of biomedical data sources (MEDLINE, life science journals, and online books), leaving out vast amounts of potentially relevant data that are difficult to retrieve and typically not accessed or utilized by biomedical science (e.g., consumer surveys reported in the media).

Alternative search strategies can be executed via computer programs that could, for example, efficiently search millions of tweets on Twitter for names of mucoactive drugs to construct a matrix of factors associated with their effectiveness and safe use, employing the #hashtags that link them. The resulting matrix of random consumer ratings for these treatments could be further refined by additional filters or via algorithmic combination with other datasets. Researchers at the University of Vermont [30] developed a social network mining approach with a tool for linking and searching drug-related literature in an effort to search for drug interaction and adverse event information.

We are at the very beginning of discovering the potential and usefulness of Big Data analyses. Expected outcomes (e.g., finding previously untapped clinical and consumer data to accelerate the development of clinical models for expectorants) offer considerable promise for economizing time and resource needs in biomedical research and should be explored.

Compliance with Ethical Standards

Conflict of Interest Dr. Albrecht is currently consulting for Reckitt Benckiser, LLC. Although no support was received for the preparation of this publication, the company has supported a related oral presentation at the American Cough Conference, 2015.

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