



A Role for Mucolytics and Expectorants in Aiding Inhaled Therapies in Asthma? [Response To Letter]

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Dear editor

We are grateful to Urakov and Urakova for their interest in our review article “Recent Insights into the Management of Inflammation in Asthma”.¹ We, in turn, read with interest their associated recent correspondence suggesting a potential role for aerosolized expectorants and mucolytics in augmenting asthma therapies such as inhaled corticosteroids (ICS).² We thank them for highlighting the relevance of mucus hypersecretion in the context of asthma. We agree that mucus hypersecretion is a potentially associated feature of numerous often problematic asthma phenotypes, including allergic fungal airways disease,³ overlap bronchiectasis,⁴ dual Chronic Obstructive Pulmonary Disease (COPD),⁵ asthmatic granulomatosis⁶ and asthma with chronic rhinosinusitis and nasal polyps.⁷ It may therefore have particular prominence in the context of more difficult-to-treat asthma and facilitate poorer asthma outcomes. Aberrant expression of gel-forming mucins such as MUC5AC and MUC5B have been identified as pivotal to the generation of abnormal mucus in asthma.⁸ Recognised guideline-advocated asthma treatments, such as the long-acting antimuscarinic agent tiotropium, are known to have potential mucus attenuating actions inhibiting mucus gland hypertrophy and decreasing the number of MUC5AC-positive goblet cells.⁹ Macrolide antibiotics have also shown efficacy in chronic asthma management through immunomodulatory actions that may encompass mucus-modifying effects.^{10,11}

The role of mucolytic agents in chronic airways diseases has long been recognised. The evidence base for the efficacy and safety of using mucolytics in conditions like COPD has been more rigorously assessed than in asthma. For example, a recent Cochrane review of mucolytics in COPD showed reductions in exacerbations, hospitalizations and disability days alongside few significant side-effects. However, improvements in quality of life or mortality were not observed.¹²

The role of mucolytic or expectorant agents in asthma therefore has potential plausibility, as does the concept raised by Urakov that such agents might confer better access for ICS and other inhaled therapies to reach the asthmatic airway epithelium by virtue of facilitating airway clearance.² At present, any supporting evidence base for such a recommendation for use in patients with asthma is limited and therefore not contained within mainstream asthma management guidelines. Small studies have previously reported the potential utility of such approaches in asthmatic patients without significant risk with regard to inhaled N-acetylcysteine in asthma.¹³ However, there was also at least one report of fatal anaphylaxis to

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intravenous N-acetylcysteine in an asthmatic patient recorded in the literature.¹⁴ More recent experimental mouse models of novel mucolytic agents demonstrated improved mucus ultrastructure, transport and protection from airflow obstruction, highlighting the possibility that these may have the potential to be developed into patient-facing therapies in the future.¹⁵ In addition, benefits of another novel mucolytic, monoterpene 1,8-cineole (eucalyptol), have been shown with regard to improvements in lung function, quality of life and nocturnal symptoms in patients with poorly controlled asthma.¹⁶ Mucus hypersecretion should be considered as part of the growing list of acknowledged treatable traits in airways diseases, but for the moment evidence-based treatment recommendations to address that trait in asthma are yet to be clearly defined.¹⁷ We would therefore suggest that the therapeutic role of mucolytics and expectorants in promoting airway clearance and improving airway deposition of inhaled treatments in specific asthma phenotypes is certainly worthy of further rigorous research. We look forward to seeing the findings of such work in the future.

Disclosure

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