When biology meets behaviour

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When biology meets behaviour: can medication adherence mask the contribution of pharmacogenetic effects in asthma?

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To the Editor:

We read the study of Ruffles *et al*. [1] with great interest. The authors undertook one of the first randomised controlled trials (RCTs) assessing the potential benefit of personalised prescription of bronchodilators according to Arg16Gly beta-2 genotype in adolescent patients with asthma. Following a 1-month run-in with inhaled corticosteroid (ICS) monotherapy, the intervention group received a bronchodilator according to their genotype, where AA and AG genotypes received an oral leukotriene antagonist (LTRA), montelukast, and GG genotype received an inhaled long-acting β_2-agonist (LABA), salmeterol. The control group received usual care based on the British Thoracic Society guidelines, where addition of a LABA is first choice when patients are uncontrolled on ICS alone. The authors found a small but significant (p=0.048) benefit on the Pediatric Asthma Quality of Life Questionnaire in the intervention group.

The authors are commended for delivering this unique study that may help us to further shape the future of personalised medicine in asthma. As with all interesting studies, it does however raise several questions to understand the results.

The authors explored the effect of a pharmacogenetically guided stratified approach in a pragmatic setting, and we wonder whether "real-life" everyday factors may have influenced the pharmacological responses observed; in particular, adherence to therapy and inhaler technique. The authors describe that 60–80% of the variability in asthma drug response may be explained by genetics [1, 2]. However, for some drugs, such as theophylline, it has been suggested that medication adherence may play a significant role in therapeutic response in contrast to genetics [3]. We acknowledge that theophylline has a narrower therapeutic interval compared to LABAs, yet importantly the inhaled route of administration of LABAs is prone to incorrect use and non-adherence [4]. We wonder if patients were assessed for inhaler adherence and whether inhaler technique was checked and patients trained, as these factors may have explained the heterogeneity in response to treatment and possibly, as reported by the authors, a lower than expected effect observed for personalised medicine in their study [1].

Generally, when aiming to understand the results of pharmacogenetically guided treatment choice on asthma outcomes, both biological and behavioural factors need to be considered (figure 1).

Ruffles *et al*. [1] explain the intervention effects primarily through the biological route of the drug response equation. Indeed, in the intervention group, based on Arg16Gly beta-2 genetics, a different pharmacological substance was chosen that could have directly impacted drug exposure and response, and as such asthma outcomes. However, inherent to receiving a different pharmacological substance, being assigned to the intervention group (*i.e.* receiving more orally administered montelukast) may have also impacted the behavioural route by achieving higher medication adherence. Generally, in the real-world, oral drug therapy results in higher adherence rates, as reported in a 2-year pragmatic RCT in asthma patients, where higher adherence with LTRA (median 74%) *versus* LABA (median 46%) was observed [5]. These real-world differences in adherence may have induced less marked differences in drug effects compared to shorter-term highly controlled RCTs, where add-on LABA showed generally more improvement in lung function measures and quality of life *versus* add-on LTRA [6, 7]. In our view, the extent to which a potential difference in adherence (as a result of randomisation to the intervention group)

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Medication adherence and inhaler technique may confound, in both a positive and a negative manner, outcomes of pharmacogenetic asthma studies. The importance of understanding patient behaviour when interpreting their biology should be emphasised. https://bit.ly/3tQdh1p

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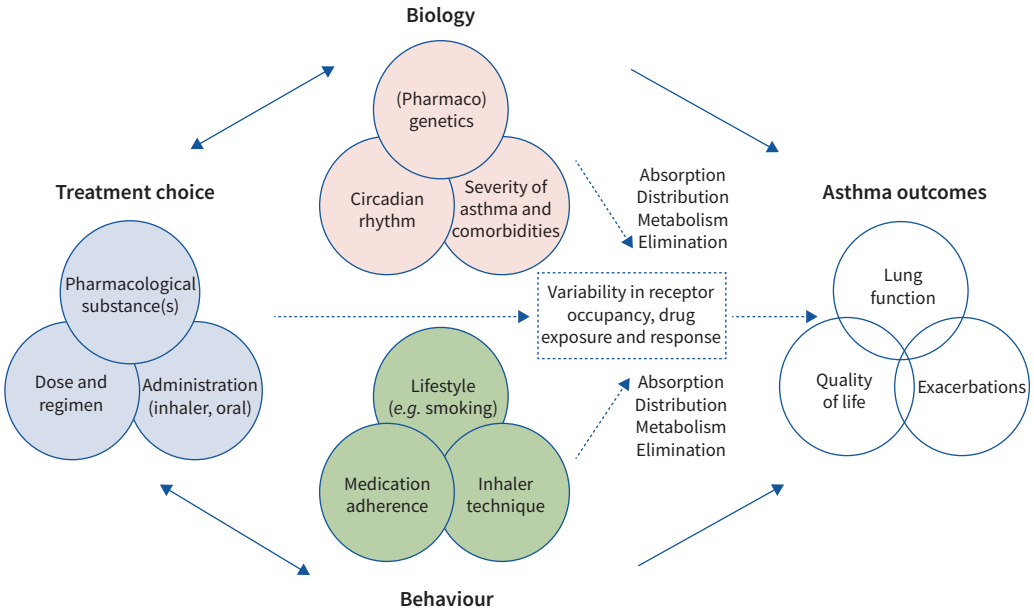

FIGURE 1 Factors that explain variability in asthma drug response.

might have played a role in explaining the outcomes of the study of Ruffles *et al*. [1] remains to be elucidated. Therefore, two issues in particular should be addressed.

First, it would be helpful to understand the post-randomisation distribution of the different asthma treatments in the intervention and control groups. Currently, only the baseline medications are provided and this hampers interpretation of the findings. It would be important to know whether the LABA was provided as a fixed dose combination inhaler with the ICS, or as separate monotherapy inhaler, the type of inhaler, with or without spacer, and whether the device type was similar or different from the ICS inhaler. Mixed device types are known to impact adherence and correct use of the inhaler [8].

Second, the authors comment on the novel methodology of their study, undertaken remotely, and this presents some additional questions related to inhaler use: 1) Was patient inhaler education performed, and if so, how and by whom? 2) How was medication adherence monitored (*e.g.* by prescription records, dose counter assessment, self-reporting or smart inhaler) and managed during the 12-month study? 3) Are differences in adherence rates available between the intervention and control groups (for both the add-on drug as background ICS)?

As medication adherence and inhaler technique in real-life are such a significant problem [9–11] they may confound, in both a positive and a negative manner, outcomes of clinical asthma studies and we assert the importance of understanding the behaviour of our patients when interpreting their biology.

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