Does adding digital inhalers to asthma triple therapy result in quadruple therapy?

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Digital technology offers a wealth of opportunities to transform asthma care [1–3]. Indeed, with ageing populations and the increasing pressure on healthcare staff and resources, digital technology may rather become a "must have" than a "nice to have". Examples of such digital technologies within the asthma area are digital inhalers. Digital inhalers are add-on or integrated sensors that can measure several aspects of patients' inhaler usage (*e.g.* actuation) and technique (*e.g.* inspiratory flow and inhaled volume). These data are typically transferred to an accompanying smartphone application that provides information and feedback to patients and their healthcare providers [4]. Importantly, digital inhalers are fulfilling a high unmet need given that in the majority of patients with asthma, adherence and inhaler technique are far from optimal, resulting in poor outcomes [5–7]. Beyond supporting education regarding inhaler adherence and technique [8, 9], data generated by digital inhalers can also support cost-effective clinical decision making, such as deciding whether or not to step up to biologics (after having adherence objectively reviewed) [10, 11]. Moreover, leveraging digital inhaler data using artificial intelligence could help in predicting exacerbations, and may support their early recognition and treatment [12]. While more rudimentary versions of digital inhalers have been around in research settings for over two decades, it is only in more recent years that digital inhalers have become increasingly smarter and connected, are mentioned in the Global Initiative for Asthma report [13], and have even become available in the daily practice of some settings. However, most digital inhaler studies so far have focused on inhalers containing inhaled corticosteroids (ICS) with or without long-acting β_2-agonists (LABA), and have been performed in relatively well-controlled clinical trial settings [4, 9, 10]. Given triple therapy has been shown to be superior to dual therapy [14], more (pragmatic) studies with digital inhalers in patients on triple therapy (*i.e.* combinations of ICS/LABA and a long-acting muscarinic antagonist (LAMA)) would be welcome. In this population, the next step-up option is biologic therapy that can be effective but comes with a considerable price tag, highlighting the importance of adequately assessing and enhancing adherence before treatment escalation is initiated. Theoretically, adding a digital inhaler to triple therapy may result in what could be called "quadruple therapy", where the behavioural benefits provided by the digital inhaler are layered on top of the pharmacological effects of the three inhaler ingredients.

In this edition of the *ERJ Open Research*, Woehrle *et al.* [15] report the results of the ADITION study. The study enrolled adult patients with asthma in Germany who had been prescribed high-dose ICS/LABA or medium/high-dose ICS/LABA/LAMA for ⩾6 months. Interestingly, proof of poor adherence and/or poor asthma control at study start was not an inclusion criterion. At the initial study visit, physicians and patients decided, using a shared decision-making process, to either start using a digital inhaler containing a fixed-dose combination (FDC) of mometasone furoate/indacaterol/glycopyrronium, or to start or continue a regular FDC of ICS/LABA/LAMA triple therapy. Subsequently, patients were followed-up for 6 months without any specific study visits and data collection restricted to real-world clinical data only (besides the

digital inhaler data). The primary endpoint of the study was a change from baseline in Asthma Control Test (ACT) score at 6 months. While the pre-calculated sample size was 250 per group, the final population included 222 patients in the digital inhaler group and 203 in the regular inhaler group, with around three quarters completing the study. Notably, given the participants were not randomised, there was a notable imbalance in study group characteristics. Most importantly, the digital inhaler group had better asthma control and a larger proportion was on previous triple therapy, meaning there was less room for improvement in this group. Additionally, in the digital inhaler group, there was a considerable decrease over time in number of patients who had digital inhaler data available (from 106 to 48 at month 6, in the total of 222 patients in this group), suggesting poor engagement with the accompanying smartphone app. Finally, following propensity score matching (to account for the disbalance in characteristics), this study found no difference in change in ACT score between the two groups, nor were notable differences in adherence observed.

A unique aspect of this study was the focus on fixed-dose triple therapy and a particular strength was its pragmatic nature, with treatment decision making mimicking real-world practice in many countries. Having said that, several limitations should also be noted. First, the inclusion criteria lacked criteria such as poor asthma control or signs of nonadherence – the obvious reasons one would consider a digital inhaler given the room for improvement. Second, the shared decision process could have resulted in self-selection of patients more eager and equipped to use digital inhalers, and therefore a lower generalisability of this group. It would have been interesting to measure (digital) health literacy of these patients and compare this to the general asthma population. This was, however, not assessed. Third, the anticipated sample size was not reached, with the COVID-19 pandemic being at least partly responsible. Moreover, the COVID-19 pandemic could have resulted in overall better asthma control and improved adherence in both groups [16, 17]. Still, for those that were included, around a quarter lost to follow up and a sharp decrease in available digital inhaler data could have resulted in further selection bias. Finally, the digital inhaler devices used did not assess inhaler technique, but merely measured intake and provided reminders in case this did not happen. Therefore, a key potential reason for uncontrolled asthma (*i.e.* poor inhaler technique) was not addressed. Overall, given the specifics of the particular inhaler and its digital add-on, these study's findings cannot be generalised to all digital inhalers. Still, several lessons can be learned.

The most important lesson learned from this study is the importance of investing in patient engagement and addressing any technical issues before starting such a study with digital inhalers. The pragmatic shared decision making approach led to initially interested patients, but their engagement seemed to wane off fairly rapidly over the course of the study. It would be of real interest to explore the underlying reasons for this, for example, using qualitative study designs such as focus groups and interviews, as has been done before [18]. Did they, for example, no longer perceive the need for digital support, perhaps because of good asthma control or after having good adherence confirmed in the first few days or weeks (highlighting good patient selection for these devices)? Were they bored with the reminders (highlighting personalisation of these)? Or were they experiencing connectivity or device malfunctioning issues (highlighting pre-trial technical and usability studies)? While all participants needed a smartphone, the study did not measure health literacy, another potential driver of good or poor device engagement. All these issues are critical for larger scale implementation of digital inhalers in daily practice. Indeed, while clinical evidence regarding their efficacy is accumulating [4, 9, 10] and some cost-effective patient groups have been identified [11], their uptake in daily practice remains rather slow and these issues may be the critical missing puzzle pieces. Beyond daily practice, another potential opportunity for more widespread application of digital inhalers is in clinical trials, where providing adherence data may be a useful "digital biomarker" [19] to better understand the efficacy–safety balance and guide personalisation of prescribed dosages. Of particular interest is their application in decentralised clinical trials, where part or all of the study procedures take place in patients' homes [20–22].

Digital inhalers and other technology are poised to play a significant role in asthma care over the next few years, and it is more a question of when exactly and how than if. However, their implementation must be approached thoughtfully to ensure they enhance rather than replace existing asthma care. For instance, they should be designed to complement the work of healthcare professionals rather than acting as a lower-value replacement [23]. For triple therapy, the ADITION study showed that adding a digital inhaler did not result in quadruple benefits, but it should not discourage us. Instead, it underscores the need to invest in identifying the right implementation pathways and understanding the key factors, such as patient engagement, usability and long-term adherence, that will make digital inhalers successful in improving patient outcomes in practice.

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