Global access and patient safety in the transition to environmentally friendly respiratory inhalers

Global access and patient safety are paramount in transition to environmentally friendly respiratory inhalers: the GINA perspective

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Climate change and its impacts on the health of our planet and its people are, deservedly, on centre stage in international discourse, and have prompted critical evaluation of all human activities that could lessen the degree and progression of these effects. Healthcare, too, is under scrutiny for its contribution to this process. Among the many issues that have been identified is the global warming potential (GWP) of gases in medical devices, including fluorinated gas (F-gas) propellants in pressurised metered-dose inhalers (pMDIs) that are often used for the treatment of airway diseases; these contribute a small but significant proportion of global greenhouse gas emissions (estimated as <0.1%).[1-9]

Many countries, including the USA, UK and several in mainland Europe, have developed policies to reduce the carbon footprint of inhalers. The chief proposed measures are to replace harmful propellants such as hydrofluoroalkane (HFA)-134a and -227ea[1,2] with safer alternatives that are under development;[4,10,11] in the meantime to choose pMDIs that have lower F-gas content;[12] and to encourage a switch to dry-powder inhalers (DPI), which do not contain propellants (assuming that the patient can use the relevant inhaler correctly).[12,13] At the same time, international action is being taken to limit use of per- and polyfluoroalkyl substances (PFAS);[14] this may affect some otherwise 'safe' propellants.

In 2022, the European Union (EU) published major draft revisions to its F-Gas Regulation,[15] including removal of the longstanding exemption for medical F-gases, and including them in an existing quota system with non-medical uses such as refrigeration and air conditioning; these quotas would sharply decrease from 2027. The proposed revisions also brought forward to 2028 a ban on export of pMDIs from the EU to countries that have not ratified the Kigali Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer.[15] However, extensive stakeholder feedback expressed concern about the risk of life-threatening shortfalls in the availability of inhaled medications within these timeframes, given the need for adequate clinical testing, regulatory approval and upscaling of manufacture and supply before the new inhalers would be widely available; these issues were also highlighted within a detailed report by the United Nations Medical and Chemical Technical Options Committee.[14] In response, recent (30/03/2023) amendments to the draft EU revisions provided for reserved quotas for pMDIs in the first two quota periods, and a slower phase-down than for other F-gases; however, the 2028 ban on exporting pMDIs was retained.[16]

The Global Initiative for Asthma (GINA), as an international non-profit organisation with a global perspective, fully supports actions like these to replace harmful propellants and

devices, but we draw attention to the serious implications of these measures for patients in countries outside the EU. This is particularly important for low- and middle-income countries (LMIC),[17] given the potential to exacerbate existing serious global inequities in healthcare[18-21] through major disruption of the availability and affordability of essential inhaled medicines. We also emphasise the evidence-based GINA strategy with combination inhaled corticosteroid (ICS)-formoterol reliever that may reduce the disproportionate morbidity and mortality from asthma in LMIC,[17,22] reduce over-use of short-acting beta2-agonist (SABA) inhalers, and bring environmental benefits at the same time; and we describe the considerations that clinicians should address in their choice of treatment and inhaler for each patient (Figure).[17]

Global access to inhaled asthma medications is essential

Inhalation remains the optimal mode of medication delivery for most patients with asthma. Besides their remarkable safety record at recommended doses, the expanding range of treatment options and progress in understanding the various strategies for their use mean that asthma deaths are a rare event in many well-resourced countries. However, access to inhaled treatments, particularly ICS-containing inhalers, is very limited in LMICs, largely accounting for the fact that 96% of asthma deaths worldwide occur in these countries.[18] Progress in improving access to treatment has been slow, with the cost of inhalers, even of generic formulations, the major limiting factor.[19]

Since the large majority of inhalers in LMICs are pMDIs,[2] a rapid transition to new propellant formulations, even if achievable in Europe, could have severe immediate consequences in LMICs, and reverse the progress already made. Likely contributors to disruption in pMDI availability and increased costs include market competition for inert gases for non-medical uses (especially for refrigeration, air-conditioning, and heat exchangers), lengthy approval processes for new medical products, and patent protection.[2,14] The development of more affordable generics may be slow. The revised draft EU Regulation[16] calls for cooperation and exchange of information between EU, member states, their authorities, and the European Medicines Agency (EMA) to ensure a smooth approval process for new pMDIs without affecting the accessibility, availability, and affordability of essential medicines; guidance by EMA was eventually published in March 2023.[23] However, the EU Regulation does not appear to take into account the complex relationships between the development of new products and their availability and affordability in LMICs. The

problem may be aggravated by the early (2028) prohibition of export of specified F-gases to countries that have not ratified the Kigali Amendment, including several LMICs.[24] Thus, licensing and availability of new pMDI formulations in LMICs is likely to follow some years after high-income countries, and they are likely to be more expensive; pMDIs with HFA propellants are also likely to become more expensive due to reduced availability of these propellants, further reducing medication access and availability in these countries. Market forces may also unpredictably affect the relative costs of pMDIs and DPIs.

The EU describes its initiatives as contributing *to the 2030 Agenda for Sustainable Development and its Sustainable Development Goals [SDGs], most prominently to "fight climate change"*.[15] However, the United Nations statement on SDGs recognises that *ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth – all while tackling climate change and working to preserve our oceans and forests*.[25] There is an unavoidable tension between these several aspirations. In describing ways to decarbonise health care in LMIC, Rasheed et al posit that the most rational and cost-effective way to achieve universal access to healthcare *and* reduce emissions is to invest in keeping people healthy.[26] GINA advises a careful approach to the currently proposed agendas to ensure that no one is left behind in the transition to safer propellants and DPIs.

Inhaler prescribing – one size does not fit all

Another proposal has been to replace pMDIs by DPIs,[3] with their lack of propellants an obvious advantage: the UK's National Institute of Health and Care Excellence (NICE) estimates the carbon footprint of DPIs to be one twenty-fifth that of currently available pMDIs, chiefly because of the absence of F-gas propellants.[13] In England, until recently, primary health networks were incentivised to switch patients from pMDIs to DPIs. However, since pMDIs represent the vast majority of inhalers globally,[2] any plan to switch to DPIs must include convincing details of how issues of access and affordability for poorer countries will be addressed and assured.

For all age-groups, selecting the right inhaler for the individual patient is crucial to asthma care, not only to reduce patients' symptom burden and risk, but also to reduce the need for emergency care or hospitalisation, which have considerable additional environmental impacts.[27-29]

Choice of inhaler involves several considerations (Figure):

- First, consider which medication(s) the patient needs to relieve and control symptoms and to prevent asthma exacerbations.

- Identify which inhaler devices are available for these medications in your country or healthcare system. Consider local availability, access, and cost to the patient. Where more than one medication is needed, a single (combination) inhaler is preferable to multiple inhalers. Also consider the patient's age, since DPIs are not suitable for most children aged ≤5 years; pMDIs with spacers will continue to be essential for this age-group and for many elderly patients.[17]

- Assess the individual's ability to use the available device(s) correctly; this may be determined by factors including physical dexterity, coordination, inspiratory flow, and cognitive status. Different inhaler types demand different inhalation techniques, and it is inadvisable to prescribe a pMDI and DPI for the same patient.[17,30] Incorrect inhaler technique increases the risk of severe asthma exacerbations.[30]

- Consider the environmental implications of the available inhaler(s). This has become an important part of inhaler selection by clinicians, and may also be a concern for patients where there is a choice between inhaler types for their asthma medication. Reference lists showing the carbon footprint of various inhalers should be provided for use in this discussion. The overall impact of inhalation devices on the environment should be considered from manufacture to disposal, including of their constituent parts, and not just propellants.[4,31] Such calculations are more complex but should be mandated, and take into account use of recyclable products and systems for collecting and recycling of used devices[4] (Box). However, clinicians need to be sensitive to the potential of placing an additional burden on the user[9] (so-called 'green guilt'), with a resultant negative effect upon adherence, asthma exacerbations and need for urgent health care.

- Consider patient satisfaction: the best inhaler for each patient is likely to be the one that they prefer and are able to use, since this promotes adherence and reduces risk of exacerbations.[17]

In follow-up visits healthcare providers should review symptom control and risk factors, any asthma exacerbations or adverse events, and check the patient's ability to use their inhaler(s) correctly.[17]

New asthma treatment strategies will limit the impact of inhalers and asthma on the environment

An additional approach to limiting the impact of asthma inhalers on the environment is to modify inhaler prescribing in line with GINA recommendations,[17] which are now adopted in a large number of countries. Past guidelines recommended initial treatment with SABA alone, contributing to over-reliance on SABA and under-use of ICS-containing medications,[32] even when available and affordable.[18-20] Several recent global surveys confirm that a large proportion of people with asthma use more than two SABA canisters per year,[33] which is closely linked with asthma exacerbations[34] and even asthma deaths.[35] The low cost and ready access to SABAs by prescription, together with over-the-counter availability in most countries, contribute to this abuse of SABA pMDIs.

Instead, the evidence-based approach recommended by GINA is that all adults and adolescents with asthma should receive an 'anti-inflammatory reliever', i.e. a combination inhaler containing a low dose of ICS plus either formoterol (a rapid-onset long-acting bronchodilator) or a SABA, rather than a SABA-only reliever.[17] With ICS-formoterol as the reliever, this approach (called 'GINA Track 1') markedly reduces severe exacerbations and urgent healthcare in adults and adolescents, compared with SABA alone, and reduces urgent healthcare compared with daily ICS plus as-needed SABA.[36] Since DPIs are the most commonly used devices for this regimen, it has a lower carbon footprint than conventional SABA-based treatment.[37] Combination ICS-SABA is available in a few countries but there is less evidence for its benefit.[17] Across treatment steps, use of an anti-inflammatory reliever will also reduce SABA use and overuse and the total number of pMDIs used globally, since 97% of SABAs are delivered by pMDI.[2] It also ensures that ICS is delivered whenever symptoms occur, which is even more important in LMICs where access to any ICS-containing treatment is limited.[18-20]

Providing access to anti-inflammatory relievers at affordable prices for all patients in all countries, whether via pMDI or DPI devices, is arguably both important and urgent,[22] and should be pursued in parallel with safer alternative propellants in asthma inhalers. In all

countries, avoidance of SABA-only treatment[32] and more judicious prescribing and routine monitoring of SABA use should be attempted.[33]

Conclusion

GINA urges authorities and clinicians to consider safety for patients as well as safety for the planet. Well-controlled asthma is best for the planet through minimising emergency healthcare utilisation and hospitalisations, which can themselves have substantial environmental impact. Achieving this involves selecting the best treatment strategy and inhaler device for each patient, and considering the global impact of regulatory changes on the safety of people with asthma in LMICs, who already bear the brunt of impact of climate change.

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Figure. Shared decision-making between health professional and patient about choice of inhalers for asthma treatment

[[Figure footnote]]

Source: Box 3-21 in GINA Strategy Report 2023. Reproduced with permission from reference 17.

Inhaled medications are the most effective treatments for asthma and are prescribed once the diagnosis has been confirmed. Any obstacle to appropriate drug selection and optimal use (e.g. access, technique, adherence, cost, patient satisfaction) may contribute to asthma exacerbations and poor control, and contribute to higher environmental impact.

Box. Research and reporting requirements to support environmentally friendly asthma management

- Environmental impact should be included in evaluations of medicines and health technologies.
- Calculations of harm must include the entire product life cycle from production to disposal.
- Manufacturers of inhalers should be required to report systematically on carbon emissions and other environmental impacts, and to provide advice to patients on safe disposal of used devices.
- Inhaler recycling programs should be established to reduce environmental impacts of inhalers.
- Research is needed to develop inhalation devices for patients who cannot benefit from currently available dry powder inhalers, such as young children and frail elderly.

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