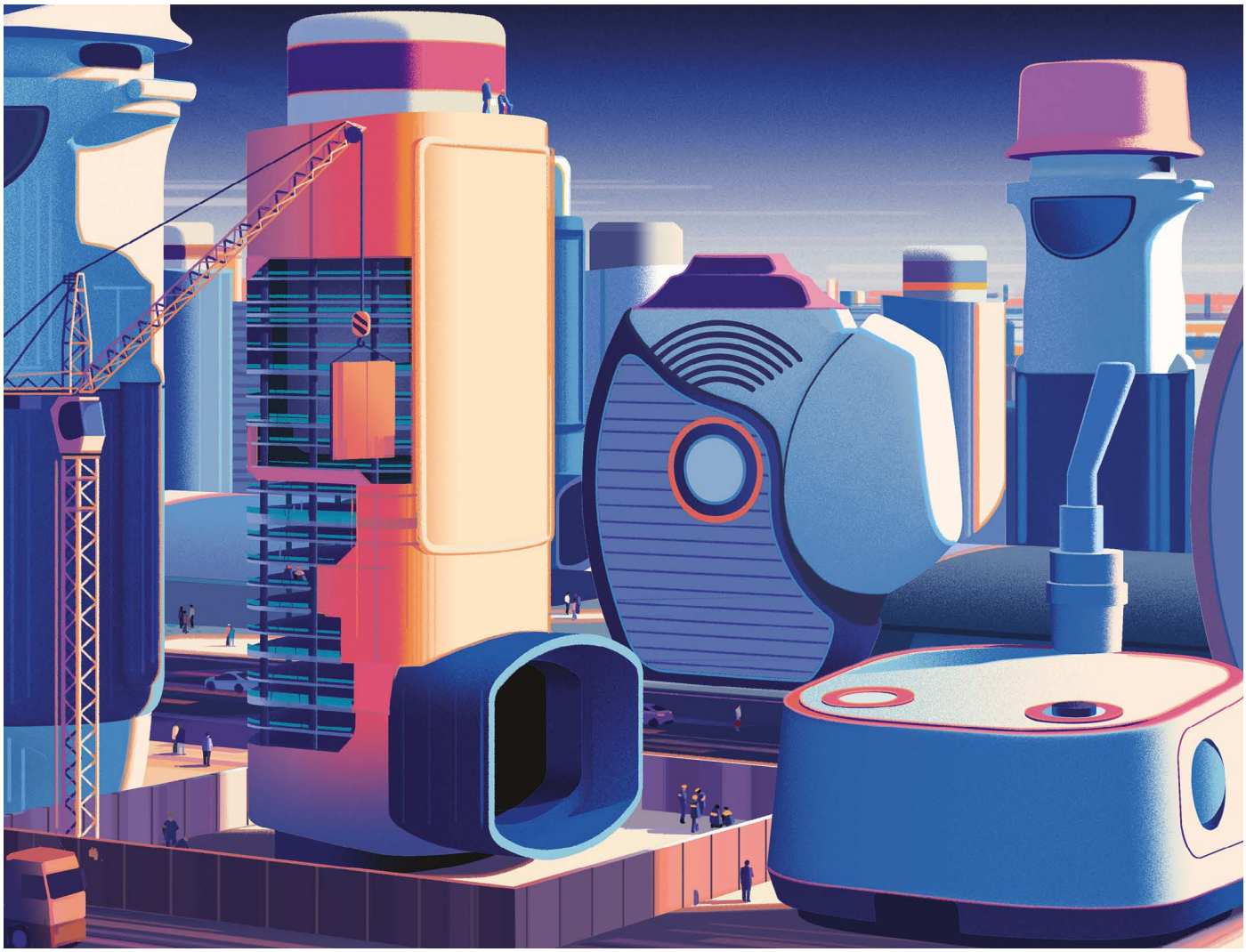
THE INHALER MAKEOVER

Environmental concerns and the perennial problem of poor inhaler technique are driving change in the devices used to deliver respiratory drugs.

By Sarah DeWeerdt



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The most important advance in inhaled therapy for chronic obstructive pulmonary disease (COPD) in the past 50 years didn't come from the discovery of a molecule or biological mechanism but instead from an international treaty that phased out the use of chlorofluorocarbons (CFCs). These chemicals, which had been found to damage the atmospheric ozone layer, were used as propellants in inhalers that deliver drugs to the lungs.

The adoption of the Montreal Protocol in September 1987 by the United Nations created a sudden need to find alternatives to CFCs, and injected a much needed spark of innovation into the inhaler field, says Stephen Stein, an aerosol scientist at manufacturing company 3M in St. Paul, Minnesota, who has been involved in inhaler research for more than 20 years. As companies raced to develop the first non-CFC inhaler, they also "took the opportunity to improve upon a technology that really had kind of stagnated over the past decades", Stein says.

The result was a plethora of inhalers and inhaled drugs that transformed the care of people with COPD. "We went from allowing patients to put up with their symptoms to

actively managing their symptoms," says Jane Scullion, a consultant respiratory nurse at University Hospitals of Leicester, UK. "If you get it right for a patient, it can transform their lives."

Now, history is repeating itself — with a twist. Although the field isn't stagnant by any stretch, it is struggling to solve long-standing problems: getting people to use their inhalers as prescribed and with the correct technique so that the medication reaches their lungs. Meanwhile, increasing attention on the environmental impacts of hydrofluoroalkane (HFA) propellants, which replaced CFCs but are themselves powerful greenhouse gases, is spurring innovations in inhaler design.

The mother of invention

The use of inhaled therapies for respiratory diseases goes back 3,500 years to ancient Egypt. But the modern-inhaler era began in 1956, when scientists at Riker Laboratories in Minnesota (Riker was acquired by 3M in 1970) introduced the Medihaler: the first portable inhaler.

The Medihaler was designed to treat asthma (inhaled therapy for COPD didn't begin until the early 1960s). It was a metered-dose inhaler (MDI), and would be familiar to current users of these devices. The user presses on a canister to release a puff of drug mixed with a propellant, while inhaling slowly and steadily to draw the medicine into the lungs.

When the Montreal Protocol was signed three decades after the Medihaler's introduction, the vast majority of inhalers in use were MDIs that used CFC gases as the propellant. Pharmaceutical companies responding to the new ban found that, to accommodate new HFA propellants, they had to tweak the design of the inhalers. This gave them an opportunity to fix some of the other long-known problems of MDIs. For example, the older devices left much of the drug in the mouth and throat, so researchers made changes to allow a larger proportion of the drug to reach the lungs, such as altering the inhalers so that they release smaller particles.

Other companies took a different path, focusing on developing a type of inhaler that uses no propellant at all. These dry-powder inhalers (DPIs) had been invented in the 1850s, but the technology had hardly advanced by the time of the CFC ban more than a century later. With no propellant to dispense their contents, DPIs instead rely on a quick, deep inhalation to draw the drug into the lungs.

Since the Montreal Protocol, other devices such as soft-mist inhalers and modern nebulizers have also joined the mix (see 'The right device for the right patient'). The device of choice varies from country to country, depending on which strategy companies in a given region pursued. For example, MDIs remain the most popular inhalers in the United Kingdom, whereas DPIs are the top choice in Scandinavia.

The original Medihaler (top) and 3M's digital smart inhaler.

3M

Persistent imperfection

As inhaler technology advanced, the range of drugs available for treating COPD expanded. Longer-acting and more-effective bronchodilators to relax and widen the airways emerged, as did a greater variety of corticosteroids to control inflammation in the lungs. By 2011, there were more than 230 different drug–device combinations on the market in Europe.

Despite these innovations, there has been little improvement in the number of people who use their inhalers correctly. For example, a comprehensive analysis of 144 studies conducted between 1975 and 2014 found that people with COPD are still as likely as patients 40 years ago to use inhalers incorrectly[1]. Mistakes can markedly reduce the effectiveness of treatment of all types of device. Overall, 31% of people in the studies reviewed had poor inhaler technique.

In some ways, the profusion of drugs and devices only increases the challenge. Most people with COPD have multiple inhalers. These devices can require different breathing techniques, which people might have trouble remembering — especially if they are struggling to breathe.

Combination inhalers, which have two or three drugs in a single device, can alleviate some of the potential for error by reducing the number of inhalers a person has to manage. But most people will still have at least two: one for daily use to prevent symptoms from starting and another to provide quick relief. Some people get these mixed up — carefully scheduling doses of their quick-relief inhaler but using their preventive inhaler only when they feel short of breath, says Amber Martirosov, a pharmacist at Wayne State University in Detroit, Michigan. And when people fail to use their preventive inhaler properly, they are at greater risk of episodes of more-severe disease known as exacerbations.

In theory, there is a simple solution to these problems: better patient education. "Once you go through the basic steps with a patient, it's really not that hard for them to use it — but you've got to take the time," Martirosov says. Often, this task falls through the cracks for physicians, nurses and pharmacists alike. It's also not a one-off job — technique can slip over time and regular reminders are needed.

Smarter devices

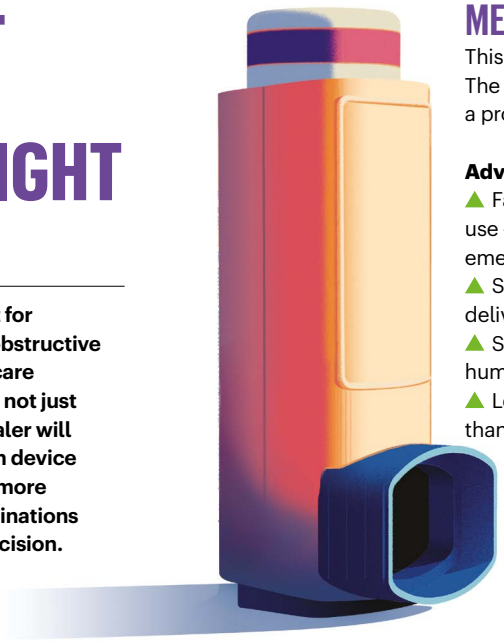
Even with good patient education, certain groups of people are likely to encounter trouble using specific types of inhalers. Some people might lack the strength and dexterity to push the canister of an MDI, or the ability to coordinate their breath with the puff of medicine. Those with memory or cognitive impairments might have trouble assembling a soft-mist inhaler. And those with severe COPD might not be able to breathe in with sufficient strength to activate a DPI.

Such physical limitations might be more common than initially thought. Over the past several years, scientists including Martirosov have found evidence that some people with advanced COPD lack the lung capacity to effectively use MDIs. "We found a subset of patients that we would teach, but they couldn't ever fix their technique," she says. "They couldn't ever improve that manoeuvre." Her team is now investigating whether switching to nebulizers is the answer for these patients.

But by and large, health-care professionals are not used to thinking about matching

THE RIGHT DEVICE FOR THE RIGHT PATIENT

When prescribing treatment for conditions such as chronic obstructive pulmonary disease, health-care professionals must consider not just the drug, but also which inhaler will best serve their patient. Each device has its drawbacks, and with more than 230 drug–device combinations available, it is not a trivial decision.

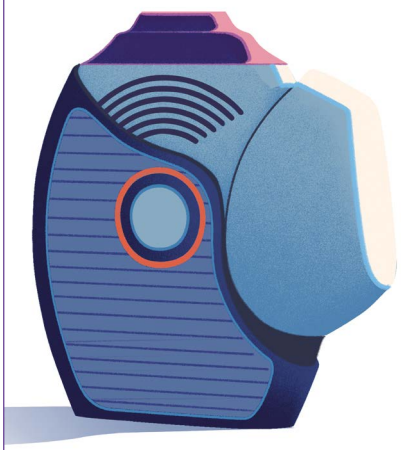


METERED-DOSE INHALER

This inhaler consists of a canister attached to a plastic mouthpiece. The user presses on the canister to release a puff of drug mixed with a propellant, while slowly inhaling to draw the drug into the lungs.

Advantages:
▲ Fast and simple to use — good for emergency treatment.
▲ Suitable for delivering most drugs.
▲ Stable in hot and humid climates.
▲ Less expensive than many inhalers.

Disadvantages:
▼ Contains environmentally damaging propellants.
▼ Requires strength and dexterity to release a puff of medicine.
▼ Might not be effective in people whose peak inspiratory force is low.
▼ Requires the patient to coordinate actuating the device and breathing in (using a holding chamber or spacer can help with this).



DRY-POWDER INHALER

Medication in these inhalers is stored in single-use capsules, or in a blister pack or reservoir from which individual doses are dispensed. Instead of a propellant, the devices rely on a quick, deep inhalation to draw the drug in.

Advantages:
▲ Suitable for those who have difficulty with coordination.
▲ Can be used to deliver most drugs.
▲ Simple to use for those with cognitive impairments.
▲ Many include a counter showing how many doses remain.

Disadvantages:
▼ The inspiratory force needed to use the inhaler can be problematic for people with advanced COPD, or those experiencing or recovering from exacerbations.
▼ Not suitable for use in hot or humid climates.
▼ Some devices require the preparation of individual doses.

SOFT-MIST INHALER

This inhaler does not contain propellant. Instead, the mechanical force of a spring turns a solution of medication into an aerosol. Twisting the base of the device compresses the spring, and pushing a button releases it. The user then inhales the aerosol through the mouthpiece.

Advantages:
▲ No need to coordinate breath and activation.
▲ Does not depend on a user's inspiratory flow rate.
▲ Targets small airways with extra-fine particles.
▲ Can be refilled.

Disadvantages:
▼ Complicated to put together.
▼ Often more costly than other devices.

NEBULIZER

These are machines that deliver medicine as a wet mist. After preparing the device with a dose of liquid medication, the patient turns the machine on and breathes in slowly through a mouthpiece or face mask until all the medicine has been delivered.

Advantages:
▲ Effective for people who can't breathe in with sufficient force to use inhalers.
▲ Good for emergencies and when higher doses of treatment are required.
▲ Suitable for those with cognitive or physical disabilities.

Disadvantages:
▼ Often bulky and inconvenient.
▼ Slower drug delivery — treatment takes 5–15 minutes.
▼ Requires regular maintenance and cleaning.

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devices to the patient. One survey of physicians found that respondents overwhelmingly placed greatest importance on the choice of drug rather than device when deciding on treatment for people with COPD; only around one-third considered the choice of device to be highly important[2]. "We've been trained for so long to just focus on the medicine and not the device," says Jill Ohar, a pulmonologist at Wake Forest School of Medicine in Winston-Salem, North Carolina, who worked on the study.

"I don't think I ever once had a lecture in my training to become a respiratory specialist on devices," agrees Omar Usmani at Imperial College London. "What people don't get is that the treatment is the drug with the device."

Some pharmaceutical companies are betting that smart inhalers with embedded electronic components can help to improve inhaler technique and adherence to treatment. Digital therapeutics companies Propeller Health in Madison, Wisconsin, and Adherium in Auckland, New Zealand, have both introduced devices that can be attached to several types of inhaler to track a person's use of medication through a mobile app.

The first stand-alone smart inhaler, the Digihaler, marketed by Teva Pharmaceutical in Petah Tikva, Israel, was approved in the United States in late 2018. The device records when a person uses the inhaler, as well as the rate at which they inhale, and sends this information to a smartphone app; patients can then review the data with their physician. A similar device, known as the Intelligent Control Inhaler, is being developed by 3M. It tracks use and tells the patient how to use it through a screen on the device. The 3M unit also troubleshoots some common mistakes when using inhalers. For example, it notifies people if they forget to shake the device before inhaling.

The Intelligent Control Inhaler is aimed at people with COPD, says Stein. "We interviewed and worked with COPD patients to make sure the system would be usable for them," he says. For example, it is designed to require an inspiratory flow rate that is achievable for most people with COPD. But the device will also be appropriate for those with asthma; 3M is now working to commercialize it with pharmaceutical partners.

Climate re-emergence

The advent of smart devices might cut against other goals for improving inhalers, however. In some health-care systems, even those of wealthy countries such as the United States, cost can be a major barrier to accessing inhalers; the high-tech versions could be even further out of reach. And although the Digihaler and Intelligent Control Inhaler are both refillable, the electronic component of each is designed to be used for only about a year. "It's hard to fathom how that could possibly be sustainable in the long term," says Alex Wilkinson, a respiratory physician at East and North Hertfordshire NHS Trust in Stevenage, UK. Even in the United Kingdom, which has a widespread inhaler recycling programme, less than 1% of devices are actually recycled — and disposable electronics will further add to the waste stream.

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An even more pressing concern is the impact of inhalers on the climate, particularly MDIs. It's long been known that the switch from CFC to HFA propellants didn't solve all the environmental problems associated with the devices. Adisa Azapagic, a sustainability analyst at the University of Manchester, UK, says that one puff from a typical MDI containing the commonly used propellant HFA-134a has a global-warming potential equivalent to 0.13 kilograms of carbon dioxide[3]. The annual greenhouse-gas emissions from MDIs in the United Kingdom are equivalent to those from roughly 600,000 diesel cars.

Over the past two years, multiple agencies in the United Kingdom, where 70% of inhalers used are MDIs, have recommended schemes to reduce the carbon footprint of inhalers by switching to other types — particularly the propellant-free DPIs.

Wilkinson and his colleagues have calculated that switching half of all inhaler prescriptions in the United Kingdom to small-carbon-footprint devices, a target set by the UK Parliament's Environmental Audit Committee, would save the equivalent of 288,000 tonnes of carbon dioxide every year[4]. That's roughly equal to taking more than 61,000 cars off the road.

The target has led to a backlash from some patient advocate groups that say inhalers are necessary medication — not a lifestyle choice like eating meat or traveling by plane — and people might be unable to use alternatives effectively, especially in an emergency. "We recognise the need to protect the environment, but it's critically important that people with asthma receive the medicines they need to stay well and avoid a life-threatening asthma attack," said Jessica Kirby, head of health advice at Asthma UK in London, in a statement responding to the study.

Some health-care professionals are cautious, too. "What concerns me is that uncritical implementation of this policy may lead to detriment to patient care," Usmani says. "We may have struggled for many months or many years to stabilize a patient with asthma or COPD," and changing their inhaler could put that at risk.

Meanwhile, companies are working to develop MDIs containing propellants with a smaller carbon footprint. Azapagic and her colleagues calculated that the global-warming impact of an inhaler containing one prominent alternative, HFA-152a, would be an order of magnitude smaller than those containing the common propellant HFC-134a.

In December, pharmaceutical company Chiesi in Parma, Italy, announced a €350-million (US$385-million) effort to bring an MDI with a climate-friendly propellant to market by 2025. Pharmaceutical giant AstraZeneca announced in January that it plans to have a similar device ready by 2025.

Wilkinson argues that in some cases, moving away from MDIs could improve care for those with COPD. For example, DPIs might be more appropriate for people who have a tendency to inhale fast and hard (the correct technique for a DPI) or who have trouble coordinating their breath with an MDI. This could also be an opportunity to reduce over-prescription of inhaled corticosteroids, about 80% of which in the United Kingdom are provided in MDIs, but which are helpful for only a subset of people with COPD (see page S12). In any case, he says, the goal is not to change treatment plans that are working for individuals, but rather to encourage physicians to rethink their default prescribing practices.

"I don't want patients to feel guilty about using MDIs," Wilkinson says. "Ultimately, we need pharma companies to step up to the plate and sort out propellants that don't have big carbon footprints. And it really looks like that's happening now."

Sarah DeWeerdt is a science writer in Seattle, Washington.

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2. Hanania, N. A. *et al. Chronic Obstr. Pulm. Dis.* **5**, 111–123 (2018).
3. Jeswani, H. K. & Azapagic, A. *J. Cleaner Prod.* **237**, 117733 (2019).
4. Wilkinson, A. J. K. *et al. BMJ Open* **9**, e028763 (2019).