BMJ Open

The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028763
Article Type:	Research
Date Submitted by the Author:	30-Jan-2019
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Keywords:	Asthma < THORACIC MEDICINE, HEALTH ECONOMICS, RESPIRATORY MEDICINE (see Thoracic Medicine), Adult thoracic medicine < THORACIC MEDICINE, Chronic airways disease < THORACIC MEDICINE

The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

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Keywords: Asthma, Chronic Airways Disease, Respiratory Medicine, Health Economics

Word count (excluding title page, abstract, references, figures and tables)**:** 3491

Abstract

Objectives: Metered dose inhalers (MDIs) contain propellants which are potent greenhouse gases. Many agencies propose a switch to alternative, low global warming potential (GWP) inhalers, such as dry powder inhalers (DPIs). We aimed to analyse the impact on greenhouse gas emissions and drug costs of making this switch.

Setting: We studied NHS prescription data from England in 2017 and collated carbon footprint data on inhalers commonly used in England.

Results: If MDIs using HFA134a are replaced with the cheapest equivalent DPI, then for every 10% of MDIs changed to DPIs, drug costs decrease by £8.2M annually. However if the brands of DPIs stay the same as 2017 prescribing patterns, for every 10% of MDIs changed to DPIs, drug costs increase by £12.7M annually. Most potential savings are due to less expensive LABA/ICS inhalers. Some reliever inhalers (e.g. Ventolin™) have a carbon footprint over 25kgCO_2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO_2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO_2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO_2e. For every 10% of MDIs changed to DPIs, 58ktCO_2e could be saved annually in England.

Conclusions: Switching to DPIs would result in large carbon savings and can be achieved alongside reduced drug costs by using less expensive brands. Substantial carbon savings can be made by using small volume HFA134a MDIs, in preference to large volume HFA134a MDIs, or those containing HFA227ea as a propellant.

Strengths and limitations of this study

- This article draws together a variety of sources of information to demonstrate significant differences in the global warming potential (GWP) of different inhalers.
- We provide practical solutions to reduce the carbon footprint of metered dose inhalers by prioritising lower volume and HFA134a metered dose inhalers (MDIs) over larger inhalers, or MDIs containing HFA227ea.
- We demonstrate that large reductions in greenhouse gas emissions are possible, alongside reduced drug costs.
- We demonstrate how drug costs could change in various different scenarios with lower greenhouse gas emissions.
- Detailed information about the carbon footprint of all inhalers is not publicly available.

Introduction

Metered-dose inhalers contain propellants, which are liquefied, compressed gases used as a driving force and an energy source for atomisation of the drug. Chlorofluorocarbons (CFCs), which were used originally, are both potent greenhouse gases (GHGs) and ozone-depleting substances, and were banned under the Montreal Protocol. They have been replaced by two hydrofluoroalkane (HFA) propellants; 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227ea).[1] Currently MDIs contribute an estimated 3.5% of the carbon footprint of the National Health Service in the UK, because HFAs are potent GHGs.[2] The UK has a high proportion of MDI use (70%) compared to less than 50% in the rest of Europe, and only about 10% in Scandinavia.[3] The most commonly used MDIs in the UK contain salbutamol reliever, though there is pressure to reduce excessive reliever use, which has been linked with poor outcomes in asthma, in favour of controller therapies.[4]

Combating climate change has been described as "the greatest public health opportunity of the 21st century".[5] HFAs are used mainly as refrigerants and are controlled under national F-gas regulations, and the Kigali Amendment to the Montreal Protocol. As F-gas use is phased out, HFA MDIs will become a significant proportion of overall HFA use, especially in the UK, because of the high level of use of MDIs.

There have been calls to switch away from HFA MDIs because of their environmental impact.[6] Effective HFA-free alternatives are already available, as DPIs and aqueous mist inhalers. Switching to inhalers with lower GWP is a key part of the NHS Sustainable Development Unit's strategy.[7] In 2017 the British Thoracic Society recommended that prescribers and patients "consider switching pMDIs to non-propellant devices whenever they are likely to be equally effective".[8] In May 2018 the UK's Environmental Audit Committee recommended the NHS set a target of reducing to 50% low-GWP inhalers by 2022.[2] In January 2019 the NHS long term plan proposed pharmacists facilitate switching patients to low GWP inhalers and claimed this could reduce the carbon footprint of the NHS by 4%.[9]

There is patchy information about the carbon footprint of inhalers. Life-cycle analysis of salbutamol MDIs has shown that 98% of its carbon footprint derives from the use-phase, when the propellant is released and this dwarfs manufacturing processes.[10,11,12] This article collates and analyses information on type and volume of emitted propellant.

A significant barrier to switching away from MDIs might be the higher "up-front" price of some DPIs; however, the price of MDIs doesn't take into account the long-term financial cost of their environmental impact. We investigate a variety of scenarios for altered inhaler prescription patterns in England, and the cost implications of switching to MDIs.

Methods

Financial analysis

We used 2017 prescription data from NHS digital website, including the number of inhalers prescribed and net ingredient cost.[13] We separated inhalers into different categories; short-acting beta agonists (SABAs), inhaled corticosteroids (ICS), long-acting beta agonists (LABAs), short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs) and combination devices. ICS were further subdivided into very low, low, medium and high strength as described in BTS/SIGN guidelines.[4] Within these categories we identified high GWP inhalers which contain HFA propellant, and low GWP inhalers which were DPIs and Respimat™ devices. The least expensive low-GWP inhaler in each inhaler category was identified, and the cost and carbon impact of changing inhalers determined in various scenarios. As Salbulin Novoliser™ is rarely used in the UK we added a scenario using Salbutamol Easyhaler™. For medium strength ICS+LABA combination inhalers we included scenarios for the cheapest once daily DPI Relvar Ellipta™, and the cheapest twice-daily dosing inhaler Fostair 100/6 Nexthaler™, which is also licensed for use as a maintenance and reliever therapy inhaler. Some discontinued inhalers and those prescribed in very low numbers (less than 500 a year) were excluded from the analysis.

Carbon footprint

Information on the amount of HFA propellant in MDIs is not publically available, so alternative sources of information were sought. Studies have estimated the contents of MDIs by weighing empty and full inhalers, and patents also provide some data. The carbon footprint was estimated by multiplying the estimated weight of HFA propellant by its 100 year GWP.

We identified the 20 most commonly prescribed MDIs using NHS prescribing data.[14] We searched google patents search engine (https://patents.google.com/) using the search terms “inhaler name” or “drug name” AND HFA or HFA134a or HFA227ea. Links and citations from relevant results were followed. We also reviewed data from the Montreal Protocol Medical Technical Options Committee.[15]

Patient and Public Involvement

A prior survey conducted in Hertfordshire,UK by one of the authors (AW) found that eighty six percent of patients agreed that both cost and carbon footprint are important factors to consider when changing inhalers.[16]

Results

Financial implications

By analysing NHS prescription data, we modelled how prescription costs would change in various different prescription scenarios.

In Model 1, we replaced MDIs with DPIs in the same proportions that brands of DPIs had been prescribed in England 2017, which we called “proportional replacement”. For example if three DPI inhalers (A, B and C) made up 50%, 30% and 20% of the DPIs in that category, then proportional replacement would switch

50% of the MDIs to DPI inhaler A, 30% to B and 20% to C. The number of MDIs declines and DPIs increase, whilst the proportions of each DPI used stays the same. In this scenario for every 10% of MDIs changed the total cost *increased* by £12.7M annually.

In Model 2, we replaced MDIs with the cheapest available equivalent DPI. In this scenario for every 10% of MDIs changed total cost *decreased* by £8.2M annually. We saw different price changes for different types of inhalers. We modelled several alternative scenarios described below and in table 1.

Short-acting beta agonists (SABA; salbutamol). In 2017 the least expensive MDI salbutamol was £1.88 versus the least expensive DPI salbutamol Salbulin Novolizer™ at £3.36 for 200-dose inhaler. Costs therefore rose £2.02M for every 10% of MDIs changed to the cheapest DPI. However the Salbulin Novolizer™ is rarely used in the UK, with only 1,015 prescriptions in 2017, so we modelled an alternative scenario in which we changed MDIs to Salbutamol Easyhaler™ instead (£3.85 per inhaler). In this model costs rose £3.01M for every 10% of inhalers changed.

Long-acting beta agonists (LABA). The least expensive LABA in 2017 was Formoterol Easyhaler™, which is similarly priced to the least expensive MDI LABA at £25.37 per inhaler. We found savings of £1.02M for every 10% of MDIs changed. For proportional replacement, costs increased by £1.47M for every 10% of MDIs changed.

Inhaled corticosteroids (ICS). We divided ICS inhalers as described in BTS/SIGN guidance into very low, low, medium and high strength inhalers.[4] We identified the least expensive equivalent DPI ICS in each category. These were Flixotide 50 Accuhaler™ (£8.54 per inhaler) one inhalation BD for very low strength, Beclometasone 200 Easyhaler™ (£16.85 per inhaler) one inhalation BD for low strength and two inhalations bd for medium strength, Budesonide 400 Easyhaler™ (£20.39 per inhaler) two inhalations BD for high strength. We found costs increased slightly; £207K for every 10% of MDIs switched to the cheapest DPI. For proportional replacement costs rose £8.25M for every 10% of MDIs changed.

LABA/ICS combination inhalers. We divided inhalers into low, medium and high strength inhaled corticosteroids. The least expensive DPI inhalers were Seretide 100 Accuhaler™ (£23.89 per inhaler), Relvar 92/22 Ellipta™ (£25.31per inhaler) and Fostair 200/6 Nexthaler™ (£33.28 per inhaler) respectively. We saw large cost savings; £10.0M saved for every 10% of MDIs switched to the least expensive DPI LABA/ICS. Because Relvar™ is a once-daily inhaler which would result in a change in dosing regimen for many patients, and is not licensed for maintenance and reliever therapy in asthma patients, we modelled an alternative scenario whereby we switched medium strength LABA/ICS combination inhalers to Fostair 100/6 Nexthaler™ (£33.42 per inhaler). In this scenario we saw more modest cost savings of £6.25M for every 10% of MDIs switched. For "proportional" replacement costs fell £668K for every 10% of MDIs changed.

Short and long-acting muscarinic antagonists and LAMA/LABA combination inhalers. We didn't change these inhalers in our model as all SAMAs are MDI and all LAMAs and LAMA+LABA devices are DPI or aqueous mist inhalers. There are potential clinical and environmental benefits from switching SAMA to LAMA inhalers .[17]

LABA/ LAMA/ICS inhalers. Two of these "triple" inhalers became available for the first time in 2017, one MDI (Trimbow™ at £47.42) and one DPI (Trelegy™ at £58.10 per inhaler). In 2017 5,211 of these inhalers were prescribed and the cost of switching from MDI to DPI was £555K for every 10% of inhalers switched.

Greenhouse gas analysis

The carbon footprint of commonly prescribed inhalers is summarised in table 2. All Salbutamol MDIs use HFA134a, with a GWP of 1,300. There are two types of salbutamol MDIs, one a small volume MDI containing alcohol as a co-solvent, which requires less HFA propellant than the large volume alcohol-free type.[18] A study comparing a large volume inhaler Ventolin™ (GSK) with small volume Salamol™ inhalerfound the weight of the contents (mainly HFA134a propellant) to be 17·32 and 7·88g respectively. A GSK patent for salbutamol MDI shows inhalers containing 18·2g and 19·8g of HFA134a.[19,20] GSK published a Carbon Trust certified carbon footprint analysis which estimated Ventolin™ to have a carbon footprint of 28kgCO_2e/inhaler, far greater than a small volume inhaler (Proventil™) at around 10kgCO_2e/inhaler. [21,10]

For SAMAs we used manufacturer's product carbon footprint data on Atrovent™ which has a product carbon footprint of 14.59kg.[12]

For ICS, comparison of two patents for beclometasone inhalers, suggest that those with alcohol use around half the HFA134a propellant (12·3g with alcohol versus 20g of HFA134a alone) of HFA134a.[22,23]

For LABA/ICS combination inhalers, one patent for Fluticasone/Salmeterol MDI (Seretide™) contained 18.2g of HFA134a.[19] GSK published carbon footprint estimates 19kgCO_2e/inhaler for their LABA, ICS/LABA and LABA MDIs. However, an FDA report on the US Advair™ brand of Fluticasone/Salmeterol MDI stated the inhaler has a net weight of just 12g/inhaler. [24]

Two LABA/ICS MDIs (Symbicort™ MDI and Flutiform™) use HFA227ea as a propellant, which has higher GWP of 3,320. A patent for Flutiform™ indicates it contains 11g (+/-0·5g) of HFA227ea, resulting in the largest carbon footprint of any inhaler at 36.5kgCO_2e/inhaler.[25]

Currently both LAMA alone, and LAMA/LABA combinations are exclusively available in the UK as DPIs. There is only one triple ICS/LAMA/LABA combination available in an MDI, and no data on propellant volume could be found (Trimbow™).

DPIs and aqueous mist inhalers

DPIs and aqueous mist inhalers (such as Respimat™) do not contain HFAs. The Medical Technical Options Committee of the United Nations estimated the carbon footprint of a DPI to be between 1·5kg and 6kg CO_2e for a 200-dose inhaler (7.5g-30g/dose) but most DPIs contain far fewer than 200 doses. [15] GSK's Carbon Trust-verified analysis of their DPIs (containing one months' treatment) found a carbon footprint of slightly less than one kilogram CO_2e/inhaler.[21] Product carbon footprint analysis of Spiriva Respimat™ published by the manufacturers found it to have a carbon footprint of 780gCO2e, but potentially lower if refill cartridges are used.[12] For our analyses we assumed a carbon footprint of 1kg CO_2e per DPI, and used the mid-point of the range of carbon footprints for each class of MDI.

We estimated the total carbon footprint of MDIs prescribed in the community in England in 2017 to be 635kt CO_2e. For every 10% of HFA MDIs changed to low-GWP devices 58ktCO_2e could be saved annually. Reaching the EAC target of 50% of inhalers being low-GWP devices by 2022, would save 288ktCO_2e every year. Reducing the proportion of high-GWP devices to 10%, as seen in Sweden, would result in carbon savings 519ktCO_2e every year.

Discussion

If prescribers switch from high GWP to the least expensive low GWP options within each therapeutic category, major financial savings could be made alongside large carbon reductions. Most of the savings are seen by switching from more expensive LABA/ICS MDIs to less expensive DPIs. These potential savings would exceed the cost of switching the larger volume of Salbutamol MDIs to DPIs, because the incremental cost per salbutamol inhaler (less than £2/inhaler) is much lower.

A second option in which prescribers switch from MDI to the DPIs according to the current proportions of brand prescribing, would be more expensive. Neither clinicians nor formularies would likely support a switch to equivalent inhalers which were more expensive. A third option in which prescribers switch from an MDI to DPI for the same branded LABA/ICS combination (e.g. Seretide™ or Fostair™) is generally either cost neutral or less expensive.

There is recent focus on cost-effectiveness, which takes into account ease of use, dose frequency and other "softer" factors that would encourage adherence, impact clinical outcomes and in turn economic cost in the real world. Poor inhaler technique is very common and greatly limits the effectiveness of inhaled medications. The most recent large meta-analysis identified fewer errors overall with DPIs, even when MDI users had spacers.[26] The Salford lung study was a large, pragmatic randomised trial that showed improved clinical outcomes in asthma and COPD patients assigned to once daily Relvar™ DPI instead of their usual inhaler (which was an MDI in 68%).[27,28] One historical matched cohort study found better asthma control in patients initiated on an MDI compared to DPI, but this study only compared Seretide

Evohaler and Accuhaler.[29] A similar matched cohort study demonstrated asthma patients can be switched from other ICS inhalers to the Easyhaler™ with no reduction in clinical effectiveness or change in cost.[30] Another similar study found better asthma control and fewer exacerbations in patients starting or increasing strength of DPIs or breath-actuated inhalers compared to pMDIs.[31] A further benefit of DPIs is that they use a dose counter, whereas Salbutamol and ICS MDIs generally do not. Patients often cannot determine when their MDIs are empty and either throw away half full inhalers, or conversely continue to use empty inhalers unknowingly.[32]

Our cost analysis has a number of limitations. Our data only includes community prescriptions in England; hospital prescriptions are not included. However, patients receiving prescriptions from hospital are likely to have more severe disease requiring combination inhalers, so the potential cost savings could be even greater. Our models do not include the impact of future changes in prescribing practice such as the recent introduction of triple LAMA/LABA/ICS inhalers.

The MDIs assessed were found to have a wide range of carbon footprints; 10-37 times that of a DPI. The UK government's DEFRA report incorrectly assumes that all inhalers contain 12g of propellant. Even among MDIs, those containing HFA227ea propellant or large volume HFA134a propellant have twice the carbon footprint or more compared to small volume MDIs. Around 6.5 million large volume MDIs for salbutamol were prescribed in England in 2016, and switching these to small volume MDIs could save 159ktCO_2e in England alone, with little clinical or patient impact.[33] Our findings provide a potentially more accurate model that could be transferred to other countries wanting to monitor and regulate MDIs in relation to carbon footprint.

Inhaler recycling has the potential to reduce the environmental impact of inhalers through recovery of propellant, although so far, uptake has been very low with less than 1% of MDIs recovered and of little measurable impact in climate terms.[11] A study of inhalers returned for recycling showed that 48% of doses remain in MDIs, compared to just 27% in DPIs.[34]

An important question is whether to switch to DPIs now, or wait for reformulated MDIs with novel low GWP propellants. Three low GWP propellants have been considered, isobutane, HFA152a and HFO 1234ea. An isobutane programme has been underway for a decade in Argentina, but not yet been commercialised. HFA152a has a lower carbon footprint (one tenth of HFA134a) and HFO1234ea zero, but both remain at early stage development.[1] Very large clinical trials will be required to establish their safety, alone and then in combination with every moiety that uses them. Transition to a novel propellant(s) would likely take a decade, although this may be cost-effective from a worldwide perspective, especially in developing countries.

Several papers assert that some patients are unable to generate the inspiratory flows necessary to activate DPIs, particularly during exacerbations. [35-36]. However, 93% of prescriptions for LAMA or LAMA/LABA devices for COPD in England are for DPIs, suggesting clinicians believe the vast majority of patients can use a DPI effectively.[14] In contrast, 94% of SABA prescriptions are for MDIs leading to a confusing mixture of inhalation techniques.[14] COPD patients whose inhaler devices use the same inhalation technique show better clinical outcomes than those prescribed devices requiring different techniques.[37] One small study examined patients' ability to use MDIs and DPIs effectively during the course of an exacerbation and found best results from an Accuhaler™ DPI which has medium resistance but is effective at relatively flow peak inspiratory flow rates of 30L/min.[38] Switching to DPI SABAs could potentially lead to a simplification of inhalation technique, an improvement in care and a reduction in carbon footprint.

Patients care about the carbon footprint of their inhalers. One survey of inhaler users found that 78% rated carbon footprint as important; equally important to them as financial cost.[16] Changing one MDI device to a DPI could save 150kg to 400kg CO_2e annually; roughly equivalent to installing wall insulation at home, recycling, or cutting out meat.[39] These are individual actions that many environmentally concerned individuals are keen to take.

Our carbon footprint results for England are consistent with other studies of MDIs in the UK (which included Scotland, Wales and Northern Ireland), which show that they contribute approximately a megaton of CO_2e to global greenhouse gas emissions. Climate change is estimated to kill 250,000 people annually by 2030, particularly vulnerable people in financially poor countries.[40] Physicians should not shy away from these issues, but reaching shared decisions with patients will be challenging and tools to assist this would be valuable.

Conclusions

Climate change is a huge and present threat to health which will disproportionately impact the poorest and most vulnerable on the planet, including people with pre-existing lung disease. Every effort must be made to minimise greenhouse gas release to protect current and future generations from the worst effects of climate change.

Switching to low GWP inhalers can be achieved whilst making financial savings in terms of drug costs. Patients, prescribers and guideline authors should carefully consider the carbon footprint of these inhalers and where they are likely to be equally effective, prioritise low GWP inhalers.

Where MDIs are considered necessary, other steps can be taken immediately to reduce their environmental impact. Smaller volume HFA134a inhalers should be prioritised over larger volume or HFA227ea-containing inhalers, manufacturers should consider phasing out the use of HFA227ea, and patients, manufacturers and clinicians should publicise and encourage inhaler recycling.

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Table 1 Financial implications of switching from MDIs to DPIs

Inhaler type (and most common example)	Number prescribed in 2017	Total cost of this type of inhaler (£)	Cheapest DPI alternative	Cost change with proportional replacement (per 10%)	Cost change with cheapest replacement (per 10%)
SABA (salbutamol MDI)	21,930,625	£58,195,683.24	Salbutamol100 Easyhaler™	£3,068,201.99	£2,021,405.23
LABA (Salmeterol 25 MDI)	700,145	£25,250,958.95	Formoterol Easyhaler™	£1,474,723.02	-£1,018,957.21
Very low dose ICS (Clenil modulite™ 50)	221,836	£82,931,128.16	Flixotide Accuhaler™ 50, 1 inh BD	£875,534.13	£ 875,534.13
Low dose ICS (Clenil modulite™ 100)	3,874,077	£36,581,577,50	Beclometasone Easyhaler™ 200, 1 inh BD	£2,461,791.16	-£213,579.26
Medium dose ICS (Clenil modulite™ 200)	1,683,466	£34,611,159.90	Beclometasone Easyhaler ™200, 2 inh BD	£3,828,332.15	-£628,752.90
High dose ICS (Clenil modulite™ 250)	287,604	£7,923,785.74	Budesonide Easyhaler ™ 400, 2 inh BD	£1,084,787.73	£173,464.97
Low dose ICS+LABA (Seretide 50 Evohaler™)	1,181,941	£32,582,876,16	Duoresp Spiromax™ 160/4.5, 1 inh bd	£749,613.82	£121,485.45
Medium dose ICS+LABA (Fostair™ 100/6 MDI)	9,467,562	£373,045,012.90	Relvar Ellipta™ 92/, 1 inh OD	£3,124,173.89	-£4,876,327.15
			OR Fostair 100/6 Nexthaler™ 2 inh BD		OR -£1,123,070.10
High dose ICS+LABA (Seretide 250 Evohaler™)	244,682	£184,212,379.80	Fostair 200/6 Nexthaler™ 2 inh BD	-£6,454,411.73	-£5,248,427.76
ICS+LAMA+LABA (Trimbow™)	5,211	£247,464.50	Trelegy Ellipta™	£ 552,801.25	£552,801.25

Table 2 Indicative carbon footprint of commonly prescribed MDIs by inhaler class

Class of inhaler (and most commonly prescribed inhaler in this class)	Indicative amount of HFA propellant per inhaler (g)	Global warming potential of HFA (over 100 years)	Carbon footprint of inhaler (g CO_2e) (range and midpoint in brackets)	Actuations per inhaler	Carbon footprint per actuation (g CO_2e)	Source
Small volume SABA (e.g. Salamol™)	6·68-8·5	1,300	8,680-11,050 (9,870)	200	43·4-55·3 (48.6 in life cycle analysis[7])	Published carbon footprint study.[9] Inhaler performance study[18]patent[41]
Large volume SABA (e.g. Ventolin™)	17·32-19·8	1,300	22,520-28,000 (25,260)	200	112-129	Inhaler performance study [18], patents [19,20], independently certified study[21]
SAMA (e.g. Atrovent™)	11	1,300	14.3kg (total product carbon footprint 14.59kg)	200	71.5	Product carbon footprint published by manufacturer[12]
LABA (e.g. Salmeterol)	12	1,300	15,600-19,000 (17,300)	120	130	Patent[42], independent study[21]
ICS (e.g. Clenil™)	11·32-20	1,300	14,700-26,000 (20,350)	200	73·5-130	Patents[22,23], independently certified study[21]
HFA134a ICS/LABA (e.g. Fostair™)	12-18·2	1,300	15,600-23,700 (19,650)	120	130-197	FDA report,[24] Patent,[19] independently certified study[21]
HFA 227ea ICS/LABA (e.g. Flutiform™)	11	3,320	36,500	120	295	Patent[25]

Declaration of Interest

AJKW – no conflict of interest to declare

RB – no conflict of interest to declare

IS - no conflict of interest to declare

JS - Dr. Smith reports personal fees from Trumpington Street Medical Practice, grants and personal fees from NHS England , personal fees from World Health Organisation Europe, personal fees from Better Value Healthcare Ltd, personal fees from Cambridgeshire County Council , personal fees from University of Cambridge, outside the submitted work; and he is married to a practicing GP in Cambridgeshire.

Data Sharing

Extra data is available by emailing alex.wilkinson2@nhs.net

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All authors meet the required criteria for authorship:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
• Drafting the work or revising it critically for important intellectual content; AND
• Final approval of the version to be published; AND
• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency Declaration

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributorship

AJKW - helped design the study, collected and analysed the data and wrote the manuscript.

JB - helped design the study, collected and analysed the data and revised the manuscript.

IS – helped analyse the data and revise the manuscript.

JS- helped design the study, collected and analysed the data and revised the manuscript.

Acknowledgements

Many thanks to Professor Ashley Woodcock of Manchester University for comments and help refining the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'

BMJ Open

The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028763.R1
Article Type:	Original research
Date Submitted by the Author:	05-Jul-2019
Complete List of Authors:	Wilkinson, Alexander; East and North Hertfordshire NHS Trust, Respiratory Department Braggins, Rory; University of Cambridge Department of Public Health and Primary Care, School of Clinical Medicine Steinbach, Ingeborg; Centre for Sustainable Healthcare Smith, James; University of Cambridge Department of Public Health and Primary Care
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics
Keywords:	Asthma < THORACIC MEDICINE, HEALTH ECONOMICS, RESPIRATORY MEDICINE (see Thoracic Medicine), Adult thoracic medicine < THORACIC MEDICINE, Chronic airways disease < THORACIC MEDICINE

The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

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Keywords: Asthma, Chronic Airways Disease, Respiratory Medicine, Health Economics

Word count (excluding title page, abstract, references, figures and tables)**:** 3491

Abstract

Objectives: Metered dose inhalers (MDIs) contain propellants which are potent greenhouse gases. Many agencies propose a switch to alternative, low global warming potential (GWP) inhalers, such as dry powder inhalers (DPIs). We aimed to analyse the impact on greenhouse gas emissions and drug costs of making this switch.

Setting: We studied NHS prescription data from England in 2017 and collated carbon footprint data on inhalers commonly used in England.

Results: If MDIs using HFA propellant are replaced with the cheapest equivalent DPI, then for every 10% of MDIs changed to DPIs, drug costs decrease by £8.2M annually. However if the brands of DPIs stay the same as 2017 prescribing patterns, for every 10% of MDIs changed to DPIs, drug costs increase by £12.7M annually. Most potential savings are due to less expensive LABA/ICS inhalers. Some reliever inhalers (e.g. Ventolin™) have a carbon footprint over 25kgCO_2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO_2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO_2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO_2e. For every 10% of MDIs changed to DPIs, 58ktCO_2e could be saved annually in England.

Conclusions: Switching to DPIs would result in large carbon savings and can be achieved alongside reduced drug costs by using less expensive brands. Substantial carbon savings can be made by using small volume HFA134a MDIs, in preference to large volume HFA134a MDIs, or those containing HFA227ea as a propellant.

Strengths and limitations of this study

- This article draws together a variety of sources of information to demonstrate significant differences in the global warming potential (GWP) of different inhalers.
- The NHS digital database provided a large, reliable dataset for us to analyse cost and greenhouse gas release in various scenarios.
- We calculated cost and greenhouse gas emissions for various scenarios in which inhalers are changed, and for different classes of inhalers (e.g. inhaled steroids, beta-agonists).
- We were unable to analyse national prescription data by diagnosis and do not know which of the inhalers might have been used for asthma, COPD or other diagnoses.
- Detailed information about the carbon footprint of all inhalers is not publicly available.

Introduction

Metered-dose inhalers contain propellants, which are liquefied, compressed gases used as a driving force and an energy source for atomisation of the drug. Chlorofluorocarbons (CFCs), which were used originally, are both potent greenhouse gases (GHGs) and ozone-depleting substances, and were banned under the Montreal Protocol. They have been replaced by two hydrofluoroalkane (HFA) propellants; 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227ea).[1] Currently MDIs contribute an estimated 3.9% of the carbon footprint of the National Health Service in the UK, because HFAs are potent GHGs.[2] The UK has a high proportion of MDI use (70%) compared to less than 50% in the rest of Europe, and only about 10% in Scandinavia.[3] The most commonly used MDIs in the UK contain salbutamol reliever, though there is pressure to reduce excessive reliever use, which has been linked with poor outcomes in asthma, in favour of controller therapies.[4]

Combating climate change has been described as "the greatest public health opportunity of the 21st century".[5] HFAs are used mainly as refrigerants and are controlled under national F-gas regulations, and the Kigali Amendment to the Montreal Protocol. As F-gas use is phased out, HFA MDIs will become a significant proportion of overall HFA use, especially in the UK, because of the high level of use of MDIs.

There have been calls to switch away from HFA MDIs because of their environmental impact.[6] Effective HFA-free alternatives are already available, as DPIs and aqueous mist inhalers. Switching to inhalers with lower global warming potential (GWP) is a key part of the NHS Sustainable Development Unit's strategy.[7] In 2017 the British Thoracic Society recommended that prescribers and patients "consider switching pMDIs to non-propellant devices whenever they are likely to be equally effective".[8] In May 2018 the UK's Environmental Audit Committee recommended the NHS set a target of reducing to 50% low-GWP inhalers by 2022.[9] In January 2019 the NHS long term plan proposed a 50% reduction in the greenhouse gas emissions from inhalers in 10 years,[10] and established an expert working group to evaluate potential strategies to achieve this.[11] There is patchy information about the carbon footprint of inhalers. Life-cycle analysis of salbutamol MDIs has shown that 95-98% of its carbon footprint derives from the use-phase, when the propellant is released and this dwarfs manufacturing processes.[12,13,14] This article collates and analyses information on type and volume of emitted propellant.

A significant barrier to switching away from MDIs might be the higher "up-front" price of some DPIs; however, the price of MDIs doesn't take into account the long-term financial cost of their environmental impact. We investigate a variety of scenarios for altered inhaler prescription patterns in England, and the cost implications of switching to MDIs.

Methods

Financial analysis

We used 2017 prescription data from NHS digital website, including the number of inhalers prescribed and net ingredient cost.[15] We separated inhalers into different categories; short-acting beta agonists (SABAs), inhaled corticosteroids (ICS), long-acting beta agonists (LABAs), short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs) and combination devices. Within these categories we identified high GWP inhalers which contain HFA propellant, and low GWP inhalers which were DPIs and Respimat™ devices. The least expensive low-GWP inhaler in each inhaler category was identified, and the cost and carbon impact of changing inhalers determined in various scenarios. Some discontinued inhalers and those prescribed in very low numbers (less than 500 a year) were excluded from the analysis.

In Model 1, we replaced MDIs with DPIs in the same proportions that brands of DPIs had been prescribed in England 2017, which we called "proportional replacement". For example if three DPI inhalers (A, B and C) made up 50%, 30% and 20% of the DPIs in that category, then proportional replacement would switch 50% of the MDIs to DPI inhaler A, 30% to B and 20% to C. The number of MDIs declines and DPIs increase, whilst the proportions of each DPI used stays the same.

In Model 2, we replaced MDIs with the cheapest available equivalent DPI. We modelled several alternative scenarios described below and in table 1.

Short-acting beta agonists (SABA; salbutamol). In 2017 the least expensive MDI salbutamol was £1.88 versus the least expensive DPI salbutamol Salbulin Novolizer™ at £3.36 for 200-dose inhaler. However the Salbulin Novolizer™ is rarely used in the UK, with only 1,015 prescriptions in 2017, so we modelled an alternative scenario in which we changed MDIs to Salbutamol Easyhaler™ instead (£3.85 per inhaler).

Long-acting beta agonists (LABA). The least expensive LABA in 2017 was Formoterol Easyhaler™, which is similarly priced to the least expensive MDI LABA at £25.37 per inhaler.

Inhaled corticosteroids (ICS). We divided ICS inhalers as described in BTS/SIGN guidance into very low, low, medium and high strength inhalers.[4] We identified the least expensive equivalent DPI ICS in each category. These were Flixotide 50 Accuhaler™ (£8.54 per inhaler) one inhalation BD for very low strength, Beclometasone 200 Easyhaler™ (£16.85 per inhaler) one inhalation BD for low strength and two inhalations bd for medium strength, Budesonide 400 Easyhaler™ (£20.39 per inhaler) two inhalations BD for high strength.

LABA/ICS combination inhalers. We divided inhalers into low, medium and high strength inhaled corticosteroids. The least expensive DPI inhalers were Seretide 100 Accuhaler™ (£23.89 per inhaler), Relvar 92/22 Ellipta™ (£25.31per inhaler) and Fostair 200/6 Nexthaler™ (£33.28 per inhaler) respectively. Relvar™ is a once-daily inhaler which would result in a change in dosing regimen for many patients, and it is also not licensed for maintenance and reliever therapy in asthma patients. We therefore modelled an alternative scenario whereby we switched medium strength LABA/ICS combination inhalers to Fostair 100/6 Nexthaler™ (£33.42 per inhaler).

Short and long-acting muscarinic antagonists and LAMA/LABA combination inhalers. We did not change these inhalers in our model as all SAMAs are MDI and all LAMAs and LAMA+LABA devices are DPI or aqueous mist inhalers. There are potential clinical and environmental benefits from switching SAMA to LAMA inhalers .[16]

LABA/ LAMA/ICS inhalers. Two of these "triple" inhalers became available for the first time in 2017, one MDI (Trimbow™ at £47.42) and one DPI (Trelegy™ at £58.10 per inhaler).

Greenhouse gas analysis

Information on the amount of HFA propellant in MDIs is not publically available, so alternative sources of information were sought. Studies have estimated the contents of MDIs by weighing empty and full inhalers, and patents also provide some data. The carbon footprint was estimated by multiplying the estimated weight of HFA propellant by its GWP. GWP is a measure of how much heat a greenhouse gas traps in the atmosphere over a specific time, relative to carbon dioxide. For the purposes of this article, we used GWP values of HFAs for a 100-year time horizon as reported in the IPCC Fifth Assessment Report.[17]

We identified the 20 most commonly prescribed MDIs using NHS prescribing data.[18] We searched google patents search engine (https://patents.google.com/) using the search terms "inhaler name" or "drug name" AND HFA or HFA134a or HFA227ea. Links and citations from relevant results were followed. We also reviewed data from the Montreal Protocol Medical Technical Options Committee.[19]

The carbon footprint of commonly prescribed inhalers is summarised in table 2. All Salbutamol MDIs use HFA134a, with a GWP of 1,300. There are two types of salbutamol MDIs, one a small volume MDI containing alcohol as a co-solvent, which requires less HFA propellant than the large volume alcohol-free type.[20] A study comparing a large volume inhaler Ventolin Evohaler™ with small volume Salamol™ inhaler found the weight of the contents (mainly HFA134a propellant) to be 17·32 and 7·88g respectively. A GSK patent for salbutamol MDI shows inhalers containing 18·2g and 19·8g of HFA134a.[21,22] GSK published a Carbon Trust certified carbon footprint analysis which estimated Ventolin™ to have a carbon footprint of 28kgCO_2e/inhaler, far greater than a small volume inhaler (Proventil™) at around 10kgCO_2e/inhaler. [23,12]

For SAMAs we used manufacturer's product carbon footprint data on Atrovent™ which has a product carbon footprint of 14.59kg.[14]

For ICS, comparison of two patents for beclometasone inhalers, suggest that those with alcohol use around half the HFA134a propellant (12·3g with alcohol versus 20g of HFA134a alone) of HFA134a.[24,25]

For LABA/ICS combination inhalers, one patent for Fluticasone/Salmeterol MDI (Seretide™) contained 18.2g of HFA134a.[21] GSK published carbon footprint estimates 19kgCO_2e/inhaler for their LABA, ICS/LABA and LABA MDIs. However, an FDA report on the US Advair™ brand of Fluticasone/Salmeterol MDI stated the inhaler has a net weight of just 12g/inhaler. [26]

Two LABA/ICS MDIs (Symbicort™ MDI and Flutiform™) use HFA227ea as a propellant, which has higher GWP of 3,320. A patent for Flutiform™ indicates it contains 11g (+/-0·5g) of HFA227ea, resulting in the largest carbon footprint of any inhaler at 36.5kgCO_2e/inhaler.[27]

Currently both LAMA alone, and LAMA/LABA combinations are exclusively available in the UK as DPIs. There is only one triple ICS/LAMA/LABA combination available in an MDI, and no data on propellant volume could be found (Trimbow™).

DPIs and aqueous mist inhalers

DPIs and aqueous mist inhalers (such as Respimat™) do not contain HFAs. The Medical Technical Options Committee of the United Nations estimated the carbon footprint of a DPI to be between 1·5kg and 6kg CO_2e for a 200-dose inhaler (7.5g-30g/dose) but most DPIs contain far fewer than 200 doses. [19] GSK's Carbon Trust-verified analysis of their DPIs (containing one months' treatment) found a carbon footprint of slightly less than one kilogram CO_2e/inhaler.[23] Product carbon footprint analysis of Spiriva Respimat™ published by the manufacturers found it to have a carbon footprint of 780gCO2e, but potentially lower if refill cartridges are used.[14] For our analyses we assumed a carbon footprint of 1kg CO_2e per DPI, and used the mid-point of the range of carbon footprints for each class of MDI.

Patient and Public Involvement

A prior survey conducted in Hertfordshire,UK by one of the authors (AW) found that eighty six percent of patients agreed that both cost and carbon footprint are important factors to consider when changing inhalers, although ease of use was considered the most important factor overall.[28]

Results

Financial implications

By analysing NHS prescription data, we modelled how prescription costs would change in various different prescription scenarios. In Model 1, we replaced MDIs with DPIs in the same proportions that brands of DPIs had been prescribed in England 2017, which we called "proportional replacement". In this scenario for every 10% of MDIs changed the total cost *increased* by £12.7M annually. In Model 2, we replaced MDIs with the cheapest available equivalent DPI. In this scenario for every 10% of MDIs changed total cost *decreased* by £8.2M annually, but we saw different price changes for different types of inhalers..

Short-acting beta agonists (SABA; salbutamol). When Salbutamol MDIs were replaced with Salbulin Novolizer™ costs rose £2.02M for every 10% of MDIs changed. As Salbulin Novolizer™ is rarely used in the UK, we modelled an alternative scenario in which we changed MDIs to Salbutamol Easyhaler™ whereby costs rose £3.01M for every 10% of inhalers changed.

*Long-acting beta agonists (LABA).*When switching to Formoterol Easyhaler™ savings of £1.02M were made for every 10% of MDIs changed. For proportional replacement, costs increased by £1.47M for every 10% of MDIs changed.

*Inhaled corticosteroids (ICS).*We found costs increased slightly; £207K for every 10% of MDIs switched to the cheapest DPI. For proportional replacement costs rose £8.25M for every 10% of MDIs changed.

LABA/ICS combination inhalers. We saw large cost savings; £10.0M saved for every 10% of MDIs switched to the least expensive DPI LABA/ICS. When switching to Fostair 100/6 Nexthaler™ instead of Relvar 92/22 Ellipta™, as Fostair also has a license for maintenance and reliever therapy, we saw more modest cost savings of £6.25M for every 10% of MDIs switched. For "proportional" replacement costs fell £668K for every 10% of MDIs changed.

LABA/ LAMA/ICS inhalers. In 2017 only 5,211 of these inhalers were prescribed and the cost of switching from MDI to DPI was £555K for every 10% of inhalers switched.

Carbon footprint

We found some reliever inhalers (e.g. Ventolin™) to have a carbon footprint over 25kgCO_2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO_2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO_2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO_2e.We estimated the total carbon footprint of MDIs prescribed in the community in England in 2017 to be 635kt CO_2e. For every 10% of HFA MDIs changed to low-GWP devices 58ktCO_2e could be saved annually. Reaching the EAC target of 50% of inhalers being low-GWP devices by 2022, would save 288ktCO_2e every year. Reducing the proportion of high-GWP devices to 10%, as seen in Sweden, would result in carbon savings 519ktCO_2e every year.

Discussion

If prescribers switch from high GWP to the least expensive low GWP options within each therapeutic category, major financial savings could be made alongside large carbon reductions. Most of the savings are seen by switching from more expensive LABA/ICS MDIs to less expensive DPIs. These potential savings would exceed the cost of switching the larger volume of Salbutamol MDIs to DPIs, because the incremental cost per salbutamol inhaler (less than £2/inhaler) is much lower.

A second option in which prescribers switch from MDI to the DPIs according to the current proportions of brand prescribing, would be more expensive. Neither clinicians nor formularies would likely support a switch to equivalent inhalers which were more expensive. A third option in which prescribers switch from an MDI to DPI for the same branded LABA/ICS combination (e.g. Seretide™ or Fostair™) is generally either cost neutral or less expensive.

There is recent focus on cost-effectiveness, which takes into account ease of use, dose frequency and other "softer" factors that would encourage adherence, impact clinical outcomes and in turn economic cost in the real world. Poor inhaler technique is very common and greatly limits the effectiveness of inhaled medications. The most recent large meta-analysis identified fewer errors overall with DPIs, even when MDI users had spacers.[29] The Salford lung study was a large, pragmatic randomised trial that showed improved clinical outcomes in asthma and COPD patients assigned to once daily Relvar™ DPI instead of their usual inhaler (which was an MDI in 68%).[30,31] One historical matched cohort study found better asthma control in patients initiated on an MDI compared to DPI, but this study only compared Seretide Evohaler and Accuhaler.[32] A similar matched cohort study demonstrated asthma patients can be switched from other ICS inhalers to the Easyhaler™ with no reduction in clinical effectiveness or change in cost.[33] Another similar study found better asthma control and fewer exacerbations in patients starting or increasing strength of DPIs or breath-actuated inhalers compared to pMDIs.[34] A further benefit of DPIs is that they use a dose counter, whereas Salbutamol and ICS MDIs generally do not. Patients often cannot determine when their MDIs are empty and either throw away half full inhalers, or conversely continue to use empty inhalers unknowingly.[35]

Our cost analysis has a number of limitations. Our data only includes community prescriptions in England; hospital prescriptions are not included. However, patients receiving prescriptions from hospital are likely to have more severe disease requiring combination inhalers, so the potential cost savings could be even greater. Our models do not include the impact of future changes in prescribing practice such as the recent introduction of triple LAMA/LABA/ICS inhalers. In reality costs are in flux and subject to market pressures, but our analysis allows comparison between treatments at a specific time point.

The MDIs assessed were found to have a wide range of carbon footprints; 10-37 times that of a DPI. The UK government reports incorrectly assumes that all inhalers contain 12g of propellant.[36] Even among MDIs, those containing HFA227ea propellant or large volume HFA134a propellant have twice the carbon footprint or more compared to small volume MDIs. Around 6.5 million large volume MDIs for salbutamol were prescribed in England in 2016, and switching these to small volume MDIs could save 159ktCO_2e in England alone, with little clinical or patient impact.[37] Our findings provide a potentially more accurate model that could be transferred to other countries wanting to monitor and regulate MDIs in relation to carbon footprint.

Inhaler recycling has the potential to reduce the environmental impact of inhalers through recovery of propellant, although so far, uptake has been very low with less than 1% of MDIs recovered and of little measurable impact in climate terms.[13] Where recycling is not available, incinerating MDIs with medicines waste is an effective strategy; this causes thermal degradation of the HFA into chemicals with far smaller global warming potential.[38] A study of inhalers returned for recycling jointly funded by GSK and NHS Grampian showed that 48% of doses remain in MDIs, compared to just 27% in DPIs.[39] This means that a significant proportion of the propellant could be captured, and that the carbon footprint of MDIs roughly halved if they were all recycled. This also highlights the importance of explaining to patients the number of doses their inhaler contains as part of inhaler technique training. Strategies to reduce greenhouse gas emmissions from MDIs are summarised in table 3.

An important question is whether to switch to DPIs now, or wait for reformulated MDIs with novel low GWP propellants. Three low GWP propellants have been considered, isobutane, HFA152a and HFO 1234ea. An isobutane programme has been underway for a decade in Argentina, but not yet been commercialised. HFA152a has a lower carbon footprint (one tenth of HFA134a) and HFO1234ea zero, but both remain at early stage development.[1] Very large clinical trials will be required to establish their safety, alone and then in combination with every moiety that uses them. Transition to a novel propellant(s) would likely take at least a decade based on experience from the transition from CFCs,[40] although this may be cost-effective from a worldwide perspective, especially in developing countries.

Several papers assert that some patients are unable to generate the inspiratory flows necessary to activate DPIs, particularly during exacerbations. [41-42]. However, 93% of prescriptions for LAMA or LAMA/LABA devices for COPD in England are for DPIs, suggesting clinicians believe the vast majority of patients can use a DPI effectively.[18] In contrast, 94% of SABA prescriptions are for MDIs leading to a confusing mixture of inhalation techniques.[18] COPD patients whose inhaler devices use the same inhalation technique show better clinical outcomes than those prescribed devices requiring different techniques.[43]One small study examined patients' ability to use MDIs and DPIs effectively during the course of an exacerbation and found best results from an Accuhaler™ DPI which has medium resistance but is effective at relatively flow peak inspiratory flow rates of 30L/min.[44] Switching to DPI SABAs could potentially lead to a simplification of inhalation technique, an improvement in care and a reduction in carbon footprint. A recent proposal suggests a reliever MDI + spacer could be kept separately in an emergency pack in case of exacerbations.[45] Whatever inhalers are used, adequate patient training and assessment of inhaler technique will be essential for efficient and effective inhaler use.[29]

Patients care about the carbon footprint of their inhalers. One survey of inhaler users found that 78% rated carbon footprint as important; equally important to them as financial cost.[28] Changing one MDI device to a DPI could save 150kg to 400kg CO_2e annually; roughly equivalent to installing wall insulation at home, recycling, or cutting out meat.[46] These are individual actions that many environmentally concerned individuals are keen to take.

Our carbon footprint results for England are consistent with other studies of MDIs in the UK (which included Scotland, Wales and Northern Ireland), which show that they contribute approximately a megaton of CO_2e to global greenhouse gas emissions. Climate change is estimated to kill 250,000 people annually by 2030, particularly vulnerable people in financially poor countries.[47] Physicians should not shy away from these issues, and tools, such as NICE's recent patient decision aid for asthma inhalers are to be welcomed.[48]

Conclusions

Climate change is a huge and present threat to health which will disproportionately impact the poorest and most vulnerable on the planet, including people with pre-existing lung disease. Every effort must be made to minimise greenhouse gas release to protect current and future generations from the worst effects of climate change.

Switching to low GWP inhalers can be achieved whilst making financial savings in terms of drug costs. Patients, prescribers and guideline authors should carefully consider the carbon footprint of these inhalers and where they are likely to be equally effective, prioritise low GWP inhalers.

Where MDIs are considered necessary, other steps can be taken immediately to reduce their environmental impact. Smaller volume HFA134a inhalers should be prioritised over larger volume or HFA227ea-containing inhalers, manufacturers should consider phasing out the use of HFA227ea, and patients, manufacturers and clinicians should publicise and encourage inhaler recycling.

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Table 1 Financial implications of switching from MDIs to DPIs

Inhaler type (and most common example)	Number prescribed in 2017	Total cost of this type of inhaler (£)	Cheapest DPI alternative	Cost change with proportional replacement (per 10%)	Cost change with cheapest replacement (per 10%)
SABA (salbutamol MDI)	21,930,625	£58,195,683.24	Salbutamol100 Easyhaler™	£3,068,201.99	£2,021,405.23
LABA (Salmeterol 25 MDI)	700,145	£25,250,958.95	Formoterol Easyhaler™	£1,474,723.02	-£1,018,957.21
Very low dose ICS (Clenil modulite™ 50)	221,836	£82,931,128.16	Flixotide Accuhaler™ 50, 1 inh BD	£875,534.13	£ 875,534.13
Low dose ICS (Clenil modulite™ 100)	3,874,077	£36,581,577,50	Beclometasone Easyhaler™ 200, 1 inh BD	£2,461,791.16	-£213,579.26
Medium dose ICS (Clenil modulite™ 200)	1,683,466	£34,611,159.90	Beclometasone Easyhaler ™200, 2 inh BD	£3,828,332.15	-£628,752.90
High dose ICS (Clenil modulite™ 250)	287,604	£7,923,785.74	Budesonide Easyhaler ™ 400, 2 inh BD	£1,084,787.73	£173,464.97
Low dose ICS+LABA (Seretide 50 Evohaler™)	1,181,941	£32,582,876,16	Duoresp Spiromax™ 160/4.5, 1 inh bd	£749,613.82	£121,485.45
Medium dose ICS+LABA (Fostair™ 100/6 MDI)	9,467,562	£373,045,012.90	Relvar Ellipta™ 92/, 1 inh OD	£3,124,173.89	-£4,876,327.15
			OR Fostair 100/6 Nexthaler™ 2 inh BD		OR -£1,123,070.10
High dose ICS+LABA (Seretide 250 Evohaler™)	244,682	£184,212,379.80	Fostair 200/6 Nexthaler™ 2 inh BD	-£6,454,411.73	-£5,248,427.76
ICS+LAMA+LABA (Trimbow™)	5,211	£247,464.50	Trelegy Ellipta™	£ 552,801.25	£552,801.25

Table 2 Indicative carbon footprint of commonly prescribed MDIs by inhaler class

Class of inhaler (and most commonly prescribed inhaler in this class)	Indicative amount of HFA propellant per inhaler (g)	Global warming potential of HFA (over 100 years)[17]	Carbon footprint of inhaler (g CO_2e) (range and midpoint in brackets)	Actuations per inhaler	Carbon footprint per actuation (g CO_2e)	Source
Small volume SABA (e.g. Salamol™)	6·68-8·5	1,300	8,680-11,050 (9,870)	200	43·4-55·3 (48.6 in life cycle analysis[7])	Published carbon footprint study.[9] Inhaler performance study[20]patent[49]
Large volume SABA (e.g. Ventolin™)	17·32-19·8	1,300	22,520-28,000 (25,260)	200	112-129	Inhaler performance study [20], patents [21,22], independently certified study[23]
SAMA (e.g. Atrovent™)	11	1,300	14.3kg (total product carbon footprint 14.59kg)	200	71.5	Product carbon footprint published by manufacturer[14]
LABA (e.g. Salmeterol)	12	1,300	15,600-19,000 (17,300)	120	130	Patent[50], independent study[23]
ICS (e.g. Clenil™)	11·32-20	1,300	14,700-26,000 (20,350)	200	73·5-130	Patents[24,25], independently certified study[23]
HFA134a ICS/LABA (e.g. Fostair™)	12-18·2	1,300	15,600-23,700 (19,650)	120	130-197	FDA report,[26] Patent,[21] independently certified study[23]
HFA 227ea ICS/LABA (e.g. Flutiform™)	11	3,320	36,500	120	295	Patent[27]

Table 3 Strategies to reduce greenhouse gas emissions from MDIs

Strategy	Effect	Potential CO2e saving
Where appropriate, switch from MDI to non-propellant inhaler	Avoids use of HFA propellants	8-36kg per inhaler
Change from large volume reliever (e.g. Ventolin Evohaler™) to small volume reliever (e.g. Salamol™)	Small volume reliever contains far less propellant	18kg per inhaler
Change from HFA227ea inhaler (e.g. Flutiform™ or Symbicort MDI™) to HFA134a inhaler	Uses lower GWP HFA propellant	20kg CO2e per inhaler
Recycle used MDIs	The plastics and aluminium are recycled and the HFA gas is captured for re-use	Estimated 4-18kg per inhaler
Return used inhalers to pharmacy after use	If the pharmacy can't recycle the MDI it will be incinerated. This causes thermal degradation of the HFA into chemicals with far smaller global warming potential.[38]	Likely to be slightly lower than recycling due to the energy inputs for incineration, and the absence of recycled materials. Estimated 3-17kg per inhaler.
If there is no dose counter, ensure your patient knows how many doses the inhaler contains	Reduce waste from disposing of half-used inhalers	Estimated to be a quarter of the inhaler's carbon footprint; roughly 4kg CO2e per inhaler.

Declaration of Interest

AJKW – no conflict of interest to declare

RB – no conflict of interest to declare

IS - no conflict of interest to declare

JS - Dr. Smith reports personal fees from Trumpington Street Medical Practice, grants and personal fees from NHS England , personal fees from World Health Organisation Europe, personal fees from Better Value Healthcare Ltd, personal fees from Cambridgeshire County Council , personal fees from University of Cambridge, outside the submitted work; and he is married to a practicing GP in Cambridgeshire.

Data Sharing

Extra data is available by emailing alex.wilkinson2@nhs.net

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Authorship statement

All authors meet the required criteria for authorship:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
• Drafting the work or revising it critically for important intellectual content; AND
• Final approval of the version to be published; AND
• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency Declaration

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributorship

AJKW - helped design the study, collected and analysed the data and wrote the manuscript.

RB - helped design the study, collected and analysed the data and revised the manuscript.

IS – helped analyse the data and revise the manuscript.

JS- helped design the study, collected and analysed the data and revised the manuscript.

Acknowledgements

Many thanks to Professor Ashley Woodcock of Manchester University for comments and help refining the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors’

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1, line 3 to 5
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2, line 1 to 38
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	page 3, line 1 to 47
		Present the study question and its relevance for health policy or practice decisions.	page 3, line 47 to 53
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 4, line 1 to 15; page 4, line 29 to 34; page 4, line 55-60; page 5, line 9-12
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4, line 16 to 27
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 11 to 15;
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 4, line 16-26
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 4, line 3-4
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not applicable
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, lines 19-24
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable.
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 4, lines 28-60; page 5, lines 10-13

Section/item	Item No	Recommendation	Reported on page No/ line No
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Financial resources: Page 4, lines 28-60; page 5, lines 10-13; Carbon costs: page 5 lines 26-page 6 line 27
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 4, lines 3-4
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 4, lines 16-23; table 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 5, lines 19-21; Page 5, lines 48-50 Page 6 lines 25-28 Table 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 4, lines 12-14; Page 5 lines 16-21;
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 6, lines 42- page 7 line40 Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 6 lines 45-51; Page 6 line 55; Page 6 line 58; Page 7 line 3-23
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 8, lines 26-35; Page 8 lines 50-51;
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or	not applicable

Section/item	Item No	Recommendation	Reported on page No/ line No
		other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 7 line 3- page 9 line 57
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Information provided via the submission system
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Information provided via the submission system

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028763.R2
Article Type:	Original research
Date Submitted by the Author:	17-Sep-2019
Complete List of Authors:	Wilkinson, Alexander; East and North Hertfordshire NHS Trust, Respiratory Department Braggins, Rory; University of Cambridge Department of Public Health and Primary Care, School of Clinical Medicine Steinbach, Ingeborg; Centre for Sustainable Healthcare Smith, James; University of Cambridge Department of Public Health and Primary Care
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics
Keywords:	Asthma < THORACIC MEDICINE, HEALTH ECONOMICS, RESPIRATORY MEDICINE (see Thoracic Medicine), Adult thoracic medicine < THORACIC MEDICINE, Chronic airways disease < THORACIC MEDICINE

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The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.

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Keywords: Asthma, Chronic Airways Disease, Respiratory Medicine, Health Economics

Word count (excluding title page, abstract, references, figures and tables)**:** 3491

Abstract

Objectives: Metered dose inhalers (MDIs) contain propellants which are potent greenhouse gases. Many agencies propose a switch to alternative, low global warming potential (GWP) inhalers, such as dry powder inhalers (DPIs). We aimed to analyse the impact on greenhouse gas emissions and drug costs of making this switch.

Setting: We studied NHS prescription data from England in 2017 and collated carbon footprint data on inhalers commonly used in England.

Design: Inhalers were separated into different categories according to their mechanisms of action (e.g. short-acting beta agonist). Within each category we identified low and high GWP inhalers and calculated the cost and carbon impact of changing to low-GWP inhalers. We modelled scenarios for swapping proportionally according to the current market share of each equivalent DPI (model 1) and switching to the lowest cost pharmaceutically equivalent DPI (model 2). We also reviewed available data on the carbon footprint of inhalers from scientific publications, independently certified reports and patents to provide more accurate carbon footprint information on different types of inhalers**.**

Results: If MDIs using HFA propellant are replaced with the cheapest equivalent DPI, then for every 10% of MDIs changed to DPIs, drug costs decrease by £8.2M annually. However if the brands of DPIs stay the same as 2017 prescribing patterns, for every 10% of MDIs changed to DPIs, drug costs increase by £12.7M annually. Most potential savings are due to less expensive LABA/ICS inhalers. Some reliever inhalers (e.g. Ventolin™) have a carbon footprint over 25kgCO_2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO_2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO_2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO_2e. For every 10% of MDIs changed to DPIs, 58ktCO_2e could be saved annually in England.

Conclusions: Switching to DPIs would result in large carbon savings and can be achieved alongside reduced drug costs by using less expensive brands. Substantial carbon savings can be made by using small volume HFA134a MDIs, in preference to large volume HFA134a MDIs, or those containing HFA227ea as a propellant.

Strengths and limitations of this study

- This article draws together a variety of sources of information to demonstrate significant differences in the global warming potential (GWP) of different inhalers.
- The NHS digital database provided a large, reliable dataset for us to analyse cost and greenhouse gas release in various scenarios.

- We calculated cost and greenhouse gas emissions for various scenarios in which inhalers are changed, and for different classes of inhalers (e.g. inhaled steroids, beta-agonists).
- We were unable to analyse national prescription data by diagnosis and do not know which of the inhalers might have been used for asthma, COPD or other diagnoses.
- Detailed information about the carbon footprint of all inhalers is not publicly available.

Introduction

Metered-dose inhalers contain propellants, which are liquefied, compressed gases used as a driving force and an energy source for atomisation of the drug. Chlorofluorocarbons (CFCs), which were used originally, are both potent greenhouse gases (GHGs) and ozone-depleting substances, and were banned under the Montreal Protocol. They have been replaced by two hydrofluoroalkane (HFA) propellants; 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227ea).[1] Currently MDIs contribute an estimated 3.9% of the carbon footprint of the National Health Service in the UK, because HFAs are potent GHGs.[2] The UK has a high proportion of MDI use (70%) compared to less than 50% in the rest of Europe, and only about 10% in Scandinavia.[3] The most commonly used MDIs in the UK contain salbutamol reliever, though there is pressure to reduce excessive reliever use, which has been linked with poor outcomes in asthma, in favour of controller therapies.[4]

Combating climate change has been described as "the greatest public health opportunity of the 21st century".[5] HFAs are used mainly as refrigerants and are controlled under national F-gas regulations, and the Kigali Amendment to the Montreal Protocol. As F-gas use is phased out, HFA MDIs will become a significant proportion of overall HFA use, especially in the UK, because of the high level of use of MDIs.

There have been calls to switch away from HFA MDIs because of their environmental impact.[6] Effective HFA-free alternatives are already available, as DPIs and aqueous mist inhalers. Switching to inhalers with lower global warming potential (GWP) is a key part of the NHS Sustainable Development Unit's strategy.[7] In 2017 the British Thoracic Society recommended that prescribers and patients "consider switching pMDIs to non-propellant devices whenever they are likely to be equally effective".[8] In May 2018 the UK's Environmental Audit Committee recommended the NHS set a target of reducing to 50% low-GWP inhalers by 2022.[9] In January 2019 the NHS long term plan proposed a 50% reduction in the greenhouse gas emissions from inhalers in 10 years,[10] and established an expert working group to evaluate potential strategies to achieve this.[11] There is patchy information about the carbon footprint of inhalers. Life-cycle analysis of salbutamol MDIs has shown that 95-98% of its carbon footprint derives from the use-phase, when the propellant is released and this dwarfs manufacturing processes.[12,13,14] This article collates and analyses information on type and volume of emitted propellant.

A significant barrier to switching away from MDIs might be the higher "up-front" price of some DPIs; however, the price of MDIs doesn't take into account the long-term financial cost of their environmental impact. We investigate a variety of scenarios for altered inhaler prescription patterns in England, and the cost implications of switching to MDIs.

Methods

Financial analysis

We used 2017 prescription data from NHS digital website, including the number of inhalers prescribed and net ingredient cost.[15] We separated inhalers into different categories; short-acting beta agonists (SABAs), inhaled corticosteroids (ICS), long-acting beta agonists (LABAs), short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs) and combination devices. Within these categories we identified high GWP inhalers which contain HFA propellant, and low GWP inhalers which were DPIs and Respimat™ devices. The least expensive low-GWP inhaler in each inhaler category was identified, and the cost and carbon impact of changing inhalers determined in various scenarios. Some discontinued inhalers and those prescribed in very low numbers (less than 500 a year) were excluded from the analysis.

In Model 1, we replaced MDIs with DPIs in the same proportions that brands of DPIs had been prescribed in England 2017, which we called "proportional replacement". For example if three DPI inhalers (A, B and C) made up 50%, 30% and 20% of the DPIs in that category, then proportional replacement would switch 50% of the MDIs to DPI inhaler A, 30% to B and 20% to C. The number of MDIs declines and DPIs increase, whilst the proportions of each DPI used stays the same.

In Model 2, we replaced MDIs with the cheapest available equivalent DPI. We modelled several alternative scenarios described below and in table 1.

Short-acting beta agonists (SABA; salbutamol). In 2017 the least expensive MDI salbutamol was £1.88 versus the least expensive DPI salbutamol Salbulin Novolizer™ at £3.36 for 200-dose inhaler. However the Salbulin Novolizer™ is rarely used in the UK, with only 1,015 prescriptions in 2017, so we modelled an alternative scenario in which we changed MDIs to Salbutamol Easyhaler™ instead (£3.85 per inhaler).

Long-acting beta agonists (LABA). The least expensive LABA in 2017 was Formoterol Easyhaler™, which is similarly priced to the least expensive MDI LABA at £25.37 per inhaler.

Inhaled corticosteroids (ICS). We divided ICS inhalers as described in BTS/SIGN guidance into very low, low, medium and high strength inhalers.[4] We identified the least expensive equivalent DPI ICS in each category. These were Flixotide 50 Accuhaler™ (£8.54 per inhaler) one inhalation BD for very low strength, Beclometasone 200 Easyhaler™ (£16.85 per inhaler) one inhalation BD for low strength and two inhalations bd for medium strength, Budesonide 400 Easyhaler™ (£20.39 per inhaler) two inhalations BD for high strength.

LABA/ICS combination inhalers. We divided inhalers into low, medium and high strength inhaled corticosteroids. The least expensive DPI inhalers were Seretide 100 Accuhaler™ (£23.89 per inhaler), Relvar 92/22 Ellipta™ (£25.31per inhaler) and Fostair 200/6 Nexthaler™ (£33.28 per inhaler) respectively. Relvar™ is a once-daily inhaler which would result in a change in dosing regimen for many patients, and it is also not licensed for maintenance and reliever therapy in asthma patients. We therefore modelled an alternative scenario whereby we switched medium strength LABA/ICS combination inhalers to Fostair 100/6 Nexthaler™ (£33.42 per inhaler).

Short and long-acting muscarinic antagonists and LAMA/LABA combination inhalers. We did not change these inhalers in our model as all SAMAs are MDI and all LAMAs and LAMA+LABA devices are DPI or aqueous mist inhalers. There are potential clinical and environmental benefits from switching SAMA to LAMA inhalers .[16]

LABA/ LAMA/ICS inhalers. Two of these "triple" inhalers became available for the first time in 2017, one MDI (Trimbow™ at £47.42) and one DPI (Trelegy™ at £58.10 per inhaler).

Greenhouse gas analysis

Information on the amount of HFA propellant in MDIs is not publically available, so alternative sources of information were sought. Studies have estimated the contents of MDIs by weighing empty and full inhalers, and patents also provide some data. The carbon footprint was estimated by multiplying the estimated weight of HFA propellant by its GWP. GWP is a measure of how much heat a greenhouse gas traps in the atmosphere over a specific time, relative to carbon dioxide. For the purposes of this article, we used GWP values of HFAs for a 100-year time horizon as reported in the IPCC Fifth Assessment Report.[17]

We identified the 20 most commonly prescribed MDIs using NHS prescribing data.[18] We searched google patents search engine (https://patents.google.com/) using the search terms "inhaler name" or "drug name" AND HFA or HFA134a or HFA227ea. Links and citations from relevant results were followed. We also reviewed data from the Montreal Protocol Medical Technical Options Committee.[19]

The carbon footprint of commonly prescribed inhalers is summarised in table 2. All Salbutamol MDIs use HFA134a, with a GWP of 1,300. There are two types of salbutamol MDIs, one a small volume MDI containing alcohol as a co-solvent, which requires less HFA propellant than the large volume alcohol-free type.[20] A study comparing a large volume inhaler Ventolin Evohaler™ with small volume Salamol™ inhaler found the weight of the contents (mainly HFA134a propellant) to be 17·32 and 7·88g respectively. A GSK patent for salbutamol MDI shows inhalers containing 18·2g and 19·8g of HFA134a.[21,22] GSK published a Carbon Trust certified carbon footprint analysis which estimated Ventolin™ to have a carbon footprint of 28kgCO_2e/inhaler, far greater than a small volume inhaler (Proventil™) at around 10kgCO_2e/inhaler. [23,12]

For SAMAs we used manufacturer's product carbon footprint data on Atrovent™ which has a product carbon footprint of 14.59kg.[14]

For ICS, comparison of two patents for beclometasone inhalers, suggest that those with alcohol use around half the HFA134a propellant (12·3g with alcohol versus 20g of HFA134a alone) of HFA134a.[24,25]

For LABA/ICS combination inhalers, one patent for Fluticasone/Salmeterol MDI (Seretide™) contained 18.2g of HFA134a.[21] GSK published carbon footprint estimates 19kgCO_2e/inhaler for their LABA, ICS/LABA and LABA MDIs. However, an FDA report on the US Advair™ brand of Fluticasone/Salmeterol MDI stated the inhaler has a net weight of just 12g/inhaler. [26]

Two LABA/ICS MDIs (Symbicort™ MDI and Flutiform™) use HFA227ea as a propellant, which has higher GWP of 3,320. A patent for Flutiform™ indicates it contains 11g (+/-0·5g) of HFA227ea, resulting in the largest carbon footprint of any inhaler at 36.5kgCO_2e/inhaler.[27]

Currently both LAMA alone, and LAMA/LABA combinations are exclusively available in the UK as DPIs. There is only one triple ICS/LAMA/LABA combination available in an MDI, and no data on propellant volume could be found (Trimbow™).

DPIs and aqueous mist inhalers

DPIs and aqueous mist inhalers (such as Respimat™) do not contain HFAs. The Medical Technical Options Committee of the United Nations estimated the carbon footprint of a DPI to be between 1·5kg and 6kg CO_2e for a 200-dose inhaler (7.5g-30g/dose) but most DPIs contain far fewer than 200 doses. [19] GSK's Carbon Trust-verified analysis of their DPIs (containing one months' treatment) found a carbon footprint of slightly less than one kilogram CO_2e/inhaler.[23] Product carbon footprint analysis of Spiriva Respimat™ published by the manufacturers found it to have a carbon footprint of 780gCO2e, but potentially lower if refill cartridges are used.[14] For our analyses we assumed a carbon footprint of 1kg CO_2e per DPI, and used the mid-point of the range of carbon footprints for each class of MDI.

Patient and Public Involvement

A prior survey conducted in Hertfordshire,UK by one of the authors (AW) found that eighty six percent of patients agreed that both cost and carbon footprint are important factors to consider when changing inhalers, although ease of use was considered the most important factor overall.[28]

Results

Financial implications

By analysing NHS prescription data, we modelled how prescription costs would change in various different prescription scenarios. In Model 1, we replaced MDIs with DPIs in the same proportions that brands of DPIs had been prescribed in England 2017, which we called "proportional replacement". In this scenario for every 10% of MDIs changed the total cost *increased* by £12.7M annually. In Model 2, we replaced MDIs with the cheapest available equivalent DPI. In this scenario for every 10% of MDIs changed total cost *decreased* by £8.2M annually, but we saw different price changes for different types of inhalers..

Short-acting beta agonists (SABA; salbutamol). When Salbutamol MDIs were replaced with Salbulin Novolizer™ costs rose £2.02M for every 10% of MDIs changed. As Salbulin Novolizer™ is rarely used in the UK, we modelled an alternative scenario in which we changed MDIs to Salbutamol Easyhaler™ whereby costs rose £3.01M for every 10% of inhalers changed.

*Long-acting beta agonists (LABA).*When switching to Formoterol Easyhaler™ savings of £1.02M were made for every 10% of MDIs changed. For proportional replacement, costs increased by £1.47M for every 10% of MDIs changed.

*Inhaled corticosteroids (ICS).*We found costs increased slightly; £207K for every 10% of MDIs switched to the cheapest DPI. For proportional replacement costs rose £8.25M for every 10% of MDIs changed.

LABA/ICS combination inhalers. We saw large cost savings; £10.0M saved for every 10% of MDIs switched to the least expensive DPI LABA/ICS. When switching to Fostair 100/6 Nexthaler™ instead of Relvar 92/22 Ellipta™, as Fostair also has a license for maintenance and reliever therapy, we saw more modest cost savings of £6.25M for every 10% of MDIs switched. For "proportional" replacement costs fell £668K for every 10% of MDIs changed.

LABA/ LAMA/ICS inhalers. In 2017 only 5,211 of these inhalers were prescribed and the cost of switching from MDI to DPI was £555K for every 10% of inhalers switched.

Carbon footprint

We found some reliever inhalers (e.g. Ventolin™) to have a carbon footprint over 25kgCO_2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO_2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO_2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO_2e.We estimated the total carbon footprint of MDIs prescribed in the community in England in 2017 to be 635kt CO_2e. For every 10% of HFA MDIs changed to low-GWP devices 58ktCO_2e could be saved annually. Reaching the EAC target of 50% of inhalers being low-GWP devices by 2022, would save 288ktCO_2e every year. Reducing the proportion of high-GWP devices to 10%, as seen in Sweden, would result in carbon savings 519ktCO_2e every year.

Discussion

If prescribers switch from high GWP to the least expensive low GWP options within each therapeutic category, major financial savings could be made alongside large carbon reductions. Most of the savings are seen by switching from more expensive LABA/ICS MDIs to less expensive DPIs. These potential savings would exceed the cost of switching the larger volume of Salbutamol MDIs to DPIs, because the incremental cost per salbutamol inhaler (less than £2/inhaler) is much lower.

A second option in which prescribers switch from MDI to the DPIs according to the current proportions of brand prescribing, would be more expensive. Neither clinicians nor formularies would likely support a switch to equivalent inhalers which were more expensive. A third option in which prescribers switch from an MDI to DPI for the same branded LABA/ICS combination (e.g. Seretide™ or Fostair™) is generally either cost neutral or less expensive.

There is recent focus on cost-effectiveness, which takes into account ease of use, dose frequency and other "softer" factors that would encourage adherence, impact clinical outcomes and in turn economic cost in the real world. Poor inhaler technique is very common and greatly limits the effectiveness of inhaled medications. The most recent large meta-analysis identified fewer errors overall with DPIs, even when MDI users had spacers.[29] The Salford lung study was a large, pragmatic randomised trial that showed improved clinical outcomes in asthma and COPD patients assigned to once daily Relvar™ DPI instead of their usual inhaler (which was an MDI in 68%).[30,31] One historical matched cohort study found better asthma control in patients initiated on an MDI compared to DPI, but this study only compared Seretide Evohaler and Accuhaler.[32] A similar matched cohort study demonstrated asthma patients can be switched from other ICS inhalers to the Easyhaler™ with no reduction in clinical effectiveness or change in cost.[33] Another similar study found better asthma control and fewer exacerbations in patients starting or increasing strength of DPIs or breath-actuated inhalers compared to pMDIs.[34] A further benefit of DPIs is that they use a dose counter, whereas Salbutamol and ICS MDIs generally do not. Patients often cannot determine when their MDIs are empty and either throw away half full inhalers, or conversely continue to use empty inhalers unknowingly.[35]

Our cost analysis has a number of limitations. Our data only includes community prescriptions in England; hospital prescriptions are not included. However, patients receiving prescriptions from hospital are likely to have more severe disease requiring combination inhalers, so the potential cost savings could be even greater. Our models do not include the impact of future changes in prescribing practice such as the recent introduction of triple LAMA/LABA/ICS inhalers. In reality costs are in flux and subject to market pressures, but our analysis allows comparison between treatments at a specific time point.

The MDIs assessed were found to have a wide range of carbon footprints; 10-37 times that of a DPI. The UK government reports incorrectly assumes that all inhalers contain 12g of propellant.[36] Even among MDIs, those containing HFA227ea propellant or large volume HFA134a propellant have twice the carbon footprint or more compared to small volume MDIs. Around 6.5 million large volume MDIs for salbutamol were prescribed in England in 2016, and switching these to small volume MDIs could save 159ktCO_2e in England alone, with little clinical or patient impact.[37] Our findings provide a potentially more accurate model that could be transferred to other countries wanting to monitor and regulate MDIs in relation to carbon footprint.

Inhaler recycling has the potential to reduce the environmental impact of inhalers through recovery of propellant, although so far uptake has been very low with less than 1% of MDIs recovered and of little measurable impact in climate terms.[13] Where recycling is not available, incinerating MDIs with medicines waste is an effective strategy; this causes thermal degradation of the HFA into chemicals with far smaller global warming potential.[38] A study of inhalers returned for recycling jointly funded by GSK and NHS Grampian showed that 48% of doses remain in MDIs, compared to just 27% in DPIs.[39] This highlights the importance of explaining to patients the number of doses their inhaler contains as part of inhaler technique training. This also means that a significant proportion of the propellant could be captured, and that the carbon footprint of MDIs potentially roughly halved if they were all recycled and the HFA propellant reused. At the end of their useful life HFA must be incinerated however, and it's possible that recycling HFAs could provide further opportunities for atmospheric release by delaying incineration. Other strategies to reduce greenhouse gas emissions from MDIs are summarised in table 3.

An important question is whether to switch to DPIs now, or wait for reformulated MDIs with novel low GWP propellants. Three low GWP propellants have been considered, isobutane, HFA152a and HFO 1234ea. An isobutane programme has been underway for a decade in Argentina, but not yet been commercialised. HFA152a has a lower carbon footprint (one tenth of HFA134a) and HFO1234ea zero, but both remain at early stage development.[1] Very large clinical trials will be required to establish their safety, alone and then in combination with every moiety that uses them. Transition to a novel propellant(s) would likely take at least a decade based on experience from the transition from CFCs,[40] although this may be cost-effective from a worldwide perspective, especially in developing countries.

Several papers assert that some patients are unable to generate the inspiratory flows necessary to activate DPIs, particularly during exacerbations. [41-42]. However, 93% of prescriptions for LAMA or LAMA/LABA devices for COPD in England are for DPIs, suggesting clinicians believe the vast majority of patients can use a DPI effectively.[18] In contrast, 94% of SABA prescriptions are for MDIs leading to a confusing mixture of inhalation techniques.[18] COPD patients whose inhaler devices use the same inhalation technique show better clinical outcomes than those prescribed devices requiring different techniques.[43]One small study examined patients' ability to use MDIs and DPIs effectively during the course of an exacerbation and found best results from an Accuhaler™ DPI which has medium resistance but is effective at relatively flow peak inspiratory flow rates of 30L/min.[44] Switching to DPI SABAs could potentially lead to a simplification of inhalation technique, an improvement in care and a reduction in carbon footprint. A recent proposal suggests a reliever MDI + spacer could be kept separately in an emergency pack in case of exacerbations.[45] Whatever inhalers are used, adequate patient training and assessment of inhaler technique will be essential for efficient and effective inhaler use.[29]

Patients care about the carbon footprint of their inhalers. One survey of inhaler users found that 78% rated carbon footprint as important; equally important to them as financial cost.[28] Changing one MDI device to a DPI could save 150kg to 400kg CO_2e annually; roughly equivalent to installing wall insulation at home, recycling, or cutting out meat.[46] These are individual actions that many environmentally concerned individuals are keen to take.

Our carbon footprint results for England are consistent with other studies of MDIs in the UK (which included Scotland, Wales and Northern Ireland), which show that they contribute approximately a megaton of CO_2e to global greenhouse gas emissions. Climate change is estimated to kill 250,000 people annually by 2030, particularly vulnerable people in financially poor countries.[47] Physicians should not shy away from these issues, and tools, such as NICE's recent patient decision aid for asthma inhalers are to be welcomed.[48]

Conclusions

Climate change is a huge and present threat to health which will disproportionately impact the poorest and most vulnerable on the planet, including people with pre-existing lung disease. Every effort must be made to minimise greenhouse gas release to protect current and future generations from the worst effects of climate change.

Switching to low GWP inhalers can be achieved whilst making financial savings in terms of drug costs. Patients, prescribers and guideline authors should carefully consider the carbon footprint of these inhalers and where they are likely to be equally effective, prioritise low GWP inhalers.

Where MDIs are considered necessary, other steps can be taken immediately to reduce their environmental impact. Smaller volume HFA134a inhalers should be prioritised over larger volume or HFA227ea-containing inhalers, manufacturers should consider phasing out the use of HFA227ea, and patients, manufacturers and clinicians should publicise and encourage inhaler recycling.

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Table 1 Financial implications of switching from MDIs to DPIs

Inhaler type (and most common example)	Number prescribed in 2017	Total cost of this type of inhaler (£)	Cheapest DPI alternative	Cost change with proportional replacement (per 10%)	Cost change with cheapest replacement (per 10%)
SABA (salbutamol MDI)	21,930,625	£58,195,683.24	Salbutamol100 Easyhaler™	£3,068,201.99	£2,021,405.23
LABA (Salmeterol 25 MDI)	700,145	£25,250,958.95	Formoterol Easyhaler™	£1,474,723.02	-£1,018,957.21
Very low dose ICS (Clenil modulite™ 50)	221,836	£82,931,128.16	Flixotide Accuhaler™ 50, 1 inh BD	£875,534.13	£ 875,534.13
Low dose ICS (Clenil modulite™ 100)	3,874,077	£36,581,577,50	Beclometasone Easyhaler™ 200, 1 inh BD	£2,461,791.16	-£213,579.26
Medium dose ICS (Clenil modulite™ 200)	1,683,466	£34,611,159.90	Beclometasone Easyhaler ™200, 2 inh BD	£3,828,332.15	-£628,752.90
High dose ICS (Clenil modulite™ 250)	287,604	£7,923,785.74	Budesonide Easyhaler ™ 400, 2 inh BD	£1,084,787.73	£173,464.97
Low dose ICS+LABA (Seretide 50 Evohaler™)	1,181,941	£32,582,876,16	Duoresp Spiromax™ 160/4.5, 1 inh bd	£749,613.82	£121,485.45
Medium dose ICS+LABA (Fostair™ 100/6 MDI)	9,467,562	£373,045,012.90	Relvar Ellipta™ 92/, 1 inh OD	£3,124,173.89	-£4,876,327.15
			OR Fostair 100/6 Nexthaler™ 2 inh BD		OR -£1,123,070.10
High dose ICS+LABA (Seretide 250 Evohaler™)	244,682	£184,212,379.80	Fostair 200/6 Nexthaler™ 2 inh BD	-£6,454,411.73	-£5,248,427.76
ICS+LAMA+LABA (Trimbow™)	5,211	£247,464.50	Trelegy Ellipta™	£ 552,801.25	£552,801.25

Table 2 Indicative carbon footprint of commonly prescribed MDIs by inhaler class

Class of inhaler (and most commonly prescribed inhaler in this class)	Indicative amount of HFA propellant per inhaler (g)	Global warming potential of HFA (over 100 years)[17]	Carbon footprint of inhaler (g CO_2e) (range and midpoint in brackets)	Actuations per inhaler	Carbon footprint per actuation (g CO_2e)	Source
Small volume SABA (e.g. Salamol™)	6·68-8·5	1,300	8,680-11,050 (9,870)	200	43·4-55·3 (48.6 in life cycle analysis[7])	Published carbon footprint study.[9] Inhaler performance study[20]patent[49]
Large volume SABA (e.g. Ventolin™)	17·32-19·8	1,300	22,520-28,000 (25,260)	200	112-129	Inhaler performance study [20], patents [21,22], independently certified study[23]
SAMA (e.g. Atrovent™)	11	1,300	14.3kg (total product carbon footprint 14.59kg)	200	71.5	Product carbon footprint published by manufacturer[14]
LABA (e.g. Salmeterol)	12	1,300	15,600-19,000 (17,300)	120	130	Patent[50], independent study[23]
ICS (e.g. Clenil™)	11·32-20	1,300	14,700-26,000 (20,350)	200	73·5-130	Patents[24,25], independently certified study[23]
HFA134a ICS/LABA (e.g. Fostair™)	12-18·2	1,300	15,600-23,700 (19,650)	120	130-197	FDA report,[26] Patent,[21] independently certified study[23]
HFA 227ea ICS/LABA (e.g. Flutiform™)	11	3,320	36,500	120	295	Patent[27]

Table 3 Strategies to reduce greenhouse gas emissions from MDIs

Strategy	Effect	Potential CO2e saving
Where appropriate, switch from MDI to non-propellant inhaler	Avoids use of HFA propellants	8-36kg per inhaler
Change from large volume reliever (e.g. Ventolin Evohaler™) to small volume reliever (e.g. Salamol™)	Small volume reliever contains far less propellant	18kg per inhaler
Change from HFA227ea inhaler (e.g. Flutiform™ or Symbicort MDI™) to HFA134a inhaler	Uses lower GWP HFA propellant	20kg CO2e per inhaler
Recycle used MDIs	The plastics and aluminium are recycled and the HFA gas is captured for re-use	Estimated 4-18kg per inhaler, although potentially risks further atmospheric release of HFA by delaying incineration.
Return used inhalers to pharmacy after use	If the pharmacy can't recycle the MDI it will be incinerated. This causes thermal degradation of the HFA into chemicals with far smaller global warming potential.[38]	Likely to be slightly lower than recycling due to the energy inputs for incineration, and the absence of recycled materials. Estimated 3-17kg per inhaler.
If there is no dose counter, ensure your patient knows how many doses the inhaler contains	Reduce waste from disposing of half-used inhalers	Estimated to be a quarter of the inhaler's carbon footprint; roughly 4kg CO2e per inhaler.

Declaration of Interest

AJKW – no conflict of interest to declare

RB – no conflict of interest to declare

IS - no conflict of interest to declare

JS - Dr. Smith reports personal fees from Trumpington Street Medical Practice, grants and personal fees from NHS England , personal fees from World Health Organisation Europe, personal fees from Better Value Healthcare Ltd, personal fees from Cambridgeshire County Council , personal fees from University of Cambridge, outside the submitted work; and he is married to a practicing GP in Cambridgeshire.

Data Sharing

Extra data is available by emailing alex.wilkinson2@nhs.net

Exclusive licence

Authorship statement

All authors meet the required criteria for authorship:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
• Drafting the work or revising it critically for important intellectual content; AND
• Final approval of the version to be published; AND
• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency Declaration

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributorship

AJKW - helped design the study, collected and analysed the data and wrote the manuscript.

RB - helped design the study, collected and analysed the data and revised the manuscript.

IS – helped analyse the data and revise the manuscript.

JS- helped design the study, collected and analysed the data and revised the manuscript.

Acknowledgements

Many thanks to Professor Ashley Woodcock of Manchester University for comments and help refining the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors’

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1, line 3 to 5
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2, line 1 to 38
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	page 3, line 1 to 47
		Present the study question and its relevance for health policy or practice decisions.	page 3, line 47 to 53
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 4, line 1 to 15; page 4, line 29 to 34; page 4, line 55-60; page 5, line 9-12
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4, line 16 to 27
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 11 to 15;
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 4, line 16-26
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 4, line 3-4
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not applicable
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, lines 19-24
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable.
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 4, lines 28-60; page 5, lines 10-13

Section/item	Item No	Recommendation	Reported on page No/ line No
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Financial resources: Page 4, lines 28-60; page 5, lines 10-13; Carbon costs: page 5 lines 26-page 6 line 27
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 4, lines 3-4
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 4, lines 16-23; table 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 5, lines 19-21; Page 5, lines 48-50 Page 6 lines 25-28 Table 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 4, lines 12-14; Page 5 lines 16-21;
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 6, lines 42- page 7 line40 Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 6 lines 45-51; Page 6 line 55; Page 6 line 58; Page 7 line 3-23
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 8, lines 26-35; Page 8 lines 50-51;
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or	not applicable

Section/item	Item No	Recommendation	Reported on page No/ line No
		other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 7 line 3- page 9 line 57
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Information provided via the submission system
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Information provided via the submission system

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist