

EXPERT OPINION

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Comparing the efficacy and safety of salmeterol/fluticasone pMDI versus its mono-components, other LABA/ICS pMDIs and salmeterol/fluticasone Diskus in patients with asthma

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Introduction: Pressurized metered dose inhalers (pMDIs) are evolving to be a very effective drug delivery option in patients with airway diseases. They offer comparable lung deposition and reduced oropharyngeal deposition similar with the dry powder inhalers. As recommended by the Global Initiative for Asthma guidelines, the ideal maintenance treatment for asthma is a combination of long acting β_2 -agonists (LABAs) and inhaled corticosteroids (ICSs). One of the available LABA/ICS combinations is the salmeterol/fluticasone propionate combination (SFC) and a plethora of evidence supports its clinical efficacy and safety.

Areas covered: This article focuses on the SFC hydrofluoroalkane pMDI and compares the efficacy and tolerability with salmeterol and fluticasone given individually, and with other fixed-dose combinations namely formoterol/fluticasone, formoterol/beclometasone and formoterol/mometasone furoate, all delivered via pMDI. Also discussed is the efficacy and tolerability of the SFC delivered via a pMDI, as compared to the SFC via Diskus.

Expert opinion: pMDIs play an important role in inhalation therapy given the low price, low maintenance and convenience of use. LABA/ICS combinations are the preferred choice of medication for asthma treatment and will remain the mainstay for the decades to come. In our opinion, pMDI should be the choice of device to administer LABA/ICS maintenance therapy, as it is already being used by the patients for reliever therapy, which may eventually improve patient adherence and compliance.

Keywords: asthma, hydrofluoroalkane, pressurized metered dose inhaler, salmeterol/fluticasone

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1. Introduction

Pressurized metered-dose inhalers (pMDIs) are the most widely prescribed devices in obstructive airway diseases – due to various factors including convenience, portability, multiple doses in a single formulation, and storage in any orientation [1,2]. Studies have shown the effectiveness of pMDIs in asthma and their ability to deliver a wide range of drugs [3]. Replacement of the traditionally used chlorofluorocarbon (CFC) with hydrofluoroalkane (HFA) propellants, in accordance with the Montreal Protocol in 1989 [4], has resulted in significant progress in the development of pMDIs [5]. HFA pMDIs are observed to be more reliable and efficient, with the aerosol plume being gentler and having a lower velocity as compared with the CFC pMDIs. These effects combined with a smaller particle size lead to less

Article highlights.

- Pressurized metered dose inhalers (pMDIs) are the most widely prescribed drug delivery devices for obstructive airways diseases. A fixed-dose combination of long-acting β_2 agonist (LABA) and inhaled corticosteroid (ICS) is the guideline-recommended treatment for patients with asthma.
- Salmeterol and fluticasone propionate in a single pMDI improves lung function and patient quality of life (QoL), and reduces daily asthma symptom scores, use of rescue medication and percentage days and nights with asthma symptoms, when compared with the mono-components and other LABA/ICS combinations.
- Salmeterol/fluticasone administered via pMDI is as efficacious and well tolerated as salmeterol/fluticasone via Diskus.
- Salmeterol and fluticasone has an established efficacy and safety profile, and it continues to be a gold standard comparator for the emerging LABA/ICS molecules in asthma.
- pMDIs with spacer are a preferred choice of maintenance treatment in patients because of their convenience, ease-of-use, portability and in continuation to the pMDIs being already used as reliever therapy.

This box summarizes key points contained in the article.

oropharyngeal deposition, reduced cold freon effect and lesser impact on the back of the throat [1,5].

The release of the aerosol from the pMDI and lung deposition is independent of the patient's inspiratory flow rate. The pressurized aerosol formulation is independent of humidity and pathogens [5]. The pMDIs deliver a uniform dose with sequential actuations, as compared with the dry powder inhalers (DPIs), which involve particle de-agglomeration that depends on the force of inhalation by the patient [5]. DPIs, therefore, require to be inhaled sharply and rapidly and this may be difficult for the elderly and very young patients with airway obstruction who may not be able to generate an inspiratory rate sufficient for optimum lung deposition [6]. Depending on the technique of use, a pMDI can deliver a drug mass of 9 – 50% to the lungs of the patients [7-12]. Critical errors were minimal with the use of a pMDI, as compared to a multi-dose DPI, a reservoir DPI and a single-dose DPI [13]. Data from European countries showed that pMDIs accounted for 56% of inhalers used, as compared with 26 and 15% of non-refillable and refillable DPIs, respectively [14].

A fixed combination of a long-acting β_2 agonist (LABA) and an inhaled corticosteroid (ICS) in a single device is recommended for the treatment of asthma by the most widely used guidelines, including the Global Initiative for Asthma (GINA) [15]. Published evidence has shown that the combination of a LABA/ICS provided greater improvement in lung function and symptom control than doubling the dose of ICS [16-21]. Salmeterol (LABA) and fluticasone (ICS) in a fixed-dose combination, when administered twice daily, increases the forced expiratory volume in one second (FEV₁)

and peak expiratory flow rate (PEFR), reduces symptoms and use of rescue salbutamol, and improves the quality of life in patients with persistent asthma [22,23]. These studies were conducted using a salmeterol/fluticasone multi-dose DPI delivery system (Diskus™).

To our knowledge, this article is the first to review the use of pMDIs in patients with asthma, with a focus on studies conducted using the salmeterol/fluticasone propionate (SFC) combination. We discuss the efficacy and tolerability of the SFC pMDI compared with the individual mono-components (fluticasone propionate and salmeterol), and with other fixed-dose LABA/ICS combinations delivered via pMDIs, including formoterol/fluticasone (F/FP), formoterol/beclomethasone and formoterol/mometasone (F/MF). This review also discusses studies comparing the SFC pMDI with the multi-dose SFC DPI (Diskus).

2. Literature search

All original articles of studies with salmeterol/fluticasone conducted in healthy volunteers and patients with asthma using the pMDI were considered relevant for the current review. PubMed was searched with three strings: 'salmeterol fluticasone MDI', 'salmeterol fluticasone pMDI' and 'salmeterol fluticasone metered dose inhaler in asthma', in ALL fields. The search was done with limits set for 'English language', 'humans' and 'clinical trials', for all articles from January 1995 to July 2014. All the articles were screened for relevance, keeping in mind the scope of the review and, additionally, a further search was carried out to check if any of the references in the primary article were found to be relevant for the scope of this review. For the purpose of discussion in the current review, earlier published reviews were also included, if found relevant, with the aim of looking at the 'salmeterol/fluticasone MDI' systematically. There were no differences between the different pMDIs used in the studies. As the aim was not a statistical interpretation of the studies, the selected articles were not assessed for risk of bias in individual studies, or the risk of bias across studies.

The articles shortlisted in the initial database search and other articles of significance (obtained from references of articles within the relevant articles) were then bucketed into categories of 'efficacy of salmeterol/fluticasone in asthma', 'safety of salmeterol/fluticasone pMDI in asthma', 'salmeterol/fluticasone pMDI versus other treatments', and 'patient satisfaction and QoL with salmeterol/fluticasone pMDI in asthma' (Figure 1). In all studies, as per the standard protocol, the patients were trained to use the device and their technique was checked for correctness. Additionally, a prospective search was done for registered clinical trials at clinicaltrials.gov for ongoing or completed studies using a salmeterol/fluticasone pMDI in patients with asthma. This has been summarized in Table 1. As the aim was not a statistical interpretation of the studies, the selected articles were not assessed for a homogenous population and uniformity in endpoints.

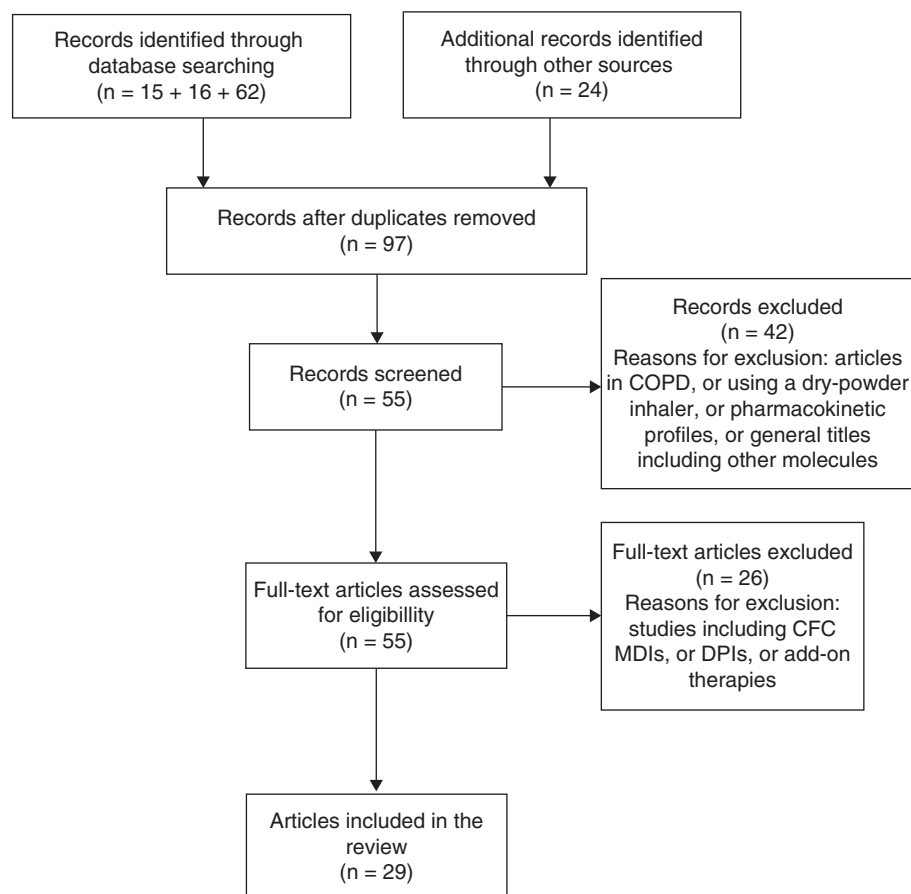


Figure 1. Literature search process.

CFC: Chlorofluorocarbon.

3. Efficacy of salmeterol/fluticasone pMDI versus mono-components and other LABA/ICS pMDIs in asthma

A summary of studies on the salmeterol/fluticasone pMDI versus other pMDIs (mono-components and LABA/ICS) in asthma is shown in Table 2.

3.1 Lung function

Studies have shown that patients using the SFC pMDI achieved $\geq 15\%$ increase in the FEV₁ within 30 min after dosing on day 1 of treatment [24-26]. Nathan *et al.* showed that patients who used the SFC pMDI had a 20% improvement from baseline in the morning pre-dose FEV₁ at the end of week 12, as compared to 9 and 8% improvements in patients on fluticasone (FP) and salmeterol (SAL) alone, respectively ($p \leq 0.001$ for all comparisons) [24]. Another study showed that the patients treated with the SFC pMDI experienced a 27% improvement from baseline in the morning pre-dose FEV₁ at the end of week 12, as compared with 18, 12 and 5% improvements in patients who received FP, SAL and placebo alone ($p \leq 0.012$), respectively [25]. Nelson *et al.* also

showed similar results, with patients on the SFC pMDI showing a 33% (0.69 L) improvement from baseline in the morning pre-dose FEV₁ at the end of week 12, as compared with 25% (0.51 L) and 22% (0.47 L) improvements with FP and SAL alone, respectively ($p \leq 0.048$) [26]. A 52-week study assessed that the mean change in the FEV₁ from baseline for low dose (two inhalations twice daily [b.i.d.] of SFC 25/50 μg), medium dose (two inhalations b.i.d. of SFC 25/125 μg) and high dose (two inhalations b.i.d. of SFC 25/250 μg) were 13, 7 and 10%, respectively [27].

In a study comparing the SFC pMDI with the F/FP pMDI, a significant change in the pre-dose FEV₁ was observed in the patients treated with the SFC than F/FP (least squares mean difference between groups: -0.061 L; $p = 0.007$), at the end of week 12 from baseline [28]. In another long-term study, there were greater increases in the mean FEV₁ values for the daily dose of SFC pMDI 50/250 μg (15%) and 50/500 μg (14.8%), than the daily dose of F/MF pMDI 10/200 μg (10.7%) and 10/400 μg (11.7%), assessed at week 52 from the baseline [29].

Studies have demonstrated greater improvements in morning and evening PEFs in patients receiving the SFC

Table 1. Summary of registered trials with salmeterol/fluticasone pMDI in asthma at clinicaltrials.gov.

Study design	Intervention	Patient population	Outcome measures	NCT number	Ref.
24-week, open-label, single group	–	Pediatric patients (aged 5 – 14 years) with asthma	AEs, SAEs, mPEFR, ePEFR, symptom-free and rescue medication-free days and nights	NCT00449046	[52]
Randomized, double-blind, double-dummy, two-period crossover	Generic SFC pMDI versus Seretide Evohaler	Adults with asthma	Total airway volume, number of deposited particles per pre-defined airway section, total airway resistance by FRI; lung function tests	NCT01795664	[53]
Open-label	SFC pMDI with dose counter versus SFC pMDI without dose counter	Adults with asthma and COPD	Patient satisfaction questionnaires	NCT00404261	[54]
16-week, randomized, double-blind, parallel group	SFC pMDI versus FP pMDI	Pediatric patients (aged 6 months to 4 years) with asthma	Overall asthma symptoms scores, asthma symptom scores at daytime and night-time, exacerbations, rescue medication use	NCT02113436	[55]
Randomized, open-label, five-way crossover study	SFC pMDI with and without spacer	Adults with asthma	Pharmacokinetic profile (area under the curve to time t and the maximum concentration)	NCT00369993	[56]
Randomized, open-label, parallel group	SFC pMDI versus FORM/BUD pMDI	Adults and adolescents with asthma	Onset of action measured by impulse oscillometry (IOS)	NCT00867737	[57]
Prospective	SFC pMDI versus SFC Diskus	Pediatric patients with asthma	Safety and efficacy for the long term	NCT01332422	[58]
Open-label	SFC pMDI or FORM/BUD DPI	Children and adults with asthma	Exhaled nitric oxide; site/mechanism(s) airflow limitation; dynamic hyperinflation	NCT01225913	[59]
Observational, prospective	SFC pMDI or FORM/BUD DPI or F/MF MDI or prednisolone	Children and adults with asthma	Exhaled nitric oxide, site of airflow limitation, dynamic hyperinflation, optical coherence tomography	NCT00576069	[60]

AEs: Adverse events; COPD: Chronic obstructive pulmonary disease; DPI: Dry powder inhaler; ePEFR: Evening peak expiratory flow rate; F/MF: Formoterol/mometasone furoate; FORM/BUD: Formoterol/budesonide; FP: Fluticasone propionate; FRI: Functional respiratory imaging; mPEFR: Morning peak expiratory flow rate; pMDI: Pressurized metered dose inhaler; SAEs: Serious adverse events; SFC: Salmeterol/fluticasone combination.

pMDI, as compared with patients receiving FP, SAL or placebo [24–26]. The mean change in baseline morning and evening PEFR at the end of treatment in three studies, in patients treated with SFC, FP, SAL and placebo, is shown in Figures 2 and 3.

At week 52, the mean change from baseline in morning PEFR was 15, 10 and 9% for low-dose (50/100 µg/day), medium-dose (50/250 µg/day) and high-dose (50/500 µg/day) SFC pMDIs, respectively [27]. In another study, mean percentage increase from baseline to week 52 in morning PEFR was observed to be 18.6% with a daily dose of SFC pMDI 50/250 µg and 9.6% with the SFC 50/500 µg [29]. A 52-week study by Bodzenta *et al.* assessed the change in lung function parameters from pre-dose baseline to 2 h post-dose at week 12. The results showed an increase of 0.354 in the least square mean forced vital capacity; 17.3 in the maximum expiratory flow rate at 25% volume (MEF₂₅); 51.7 in MEF₅₀ and 93.5 in MEF₇₅, from baseline [28].

3.2 Daily asthma symptom scores

Improvements in the mean asthma symptom scores, from baseline to the end-of-treatment period, have shown varied results in the studies. Pearlman *et al.* observed that the mean asthma symptom scores of the patients treated with the SFC pMDI was significantly reduced, indicating improvement, as compared with FP and SAL given individually (–1.0 vs –0.3 and –0.4 with FP and SAL, respectively; $p < 0.001$), from baseline to week 12 [25]. Patients using the SFC pMDI had a significantly reduced mean asthma symptom score against the placebo group (–0.5 vs 0.5; $p < 0.001$) [24]. Similar results were also shown by Nelson *et al.*, where the improvement in mean asthma symptom scores were somewhat greater after treatment with the SFC pMDI, as compared with FP and SAL (–1.0 vs –0.8 and –0.8, respectively, from baseline to week 12) [26]. Maspero *et al.* in a 52-week study reported an improvement of 45% with a daily dose of SFC pMDI 50/250 µg and 48.2% with 50/500 µg in the mean 24-h total asthma

Table 2. Summary of studies on the salmeterol/fluticasone pMDI versus other pMDIs (mono-components and LABA/ICS) in asthma.

Study combination (dose)	Comparator combination (dose)	Study design	N; patient population	Outcomes	Ref.
SFC HFA (21/44 µg, two inhalations, b.i.d.)	FP CFC (44 µg) or SAL CFC (21 µg), two inhalations, b.i.d.	12 weeks, R, PG	283; persistent asthma	Improvements with the SFC pMDI in morning pre-dose FEV ₁ , mPEFR, ePEFR, asthma symptom scores, percentage days with no asthma symptoms and rescue-free days	[26]
SFC HFA (21/44 µg, two inhalations, b.i.d.)	FP CFC (44 µg); SAL CFC (21 µg), two inhalations, b.i.d.	12 weeks, R, DB, PG, PC	360; persistent asthma	Improvements with the SFC pMDI in mPEFR and ePEFR, rescue salbutamol use, and asthma symptom scores	[25]
SFC HFA (21/110 µg, two inhalations, b.i.d.)	FP CFC (110 µg); SAL CFC (21 µg), two inhalations, b.i.d.	12 weeks, R, DB, PC, PG	365; persistent asthma	Improvements with the SFC pMDI in morning pre-dose FEV ₁ , mPEFR, ePEFR, asthma symptom scores and rescue salbutamol use	[24]
SFC pMDI (21/44 or 21/110 µg, two inhalations, b.i.d.)	SAL (21 µg) and FP (44 or 110 µg), two inhalations, b.i.d.	12 weeks, R, DB, PC	720; persistent asthma	Clinically meaningful improvements with both doses of the SFC pMDI in AQLQ scores from baseline	[31]
SFC HFA (25/50, 25/125, or 25/250 µg, two inhalations, b.i.d.)	-	52 weeks, OL, PG	325; persistent asthma	Improvements in FEV ₁ , PEFR and reduction in rescue salbutamol use with the SFC pMDI in all three groups	[27]
SFC (25/125 µg, two inhalations, b.i.d.)	-	OL	228; asthma/COPD	Increased patient satisfaction, including ease of use, convenience, assurance and improved control of the disease	[30]
SFC (25/125 or 25/250 µg, two inhalations, b.i.d.)	F/MF (5/100 or 5/200 µg, two inhalations, b.i.d.)	52 weeks, R, PG, OL, EB	404; persistent asthma	Improvements in FEV ₁ , PEFR, asthma symptom scores, proportion of asthma-free days and nights and need for rescue salbutamol use	[29]
SFC (25/50 or 25/125 µg, two inhalations, b.i.d.)	F/FP (5/50 or 5/125 µg, two inhalations, b.i.d.)	12 weeks, RMD, OL, PG	202; mild-to-moderate severe asthma	Improvements with the SFC pMDI in pre-dose FEV ₁ , change from pre-dose FEV ₁ at baseline to 2-h post-dose FEV ₁ at week 12, and FVC, MEF ₂₅ , MEF ₅₀ , MEF ₇₅ and PEFR; and asthma symptom scores, rescue salbutamol use and AQLQ	[28]
SFC (25/125 µg, two inhalations, b.i.d.)	F/BDP (6/100 µg, two inhalations, b.i.d.)	12 weeks, R, DB, PG	228; moderate-to-severe asthma	Improvements in morning pre-dose PEF in last 2 weeks of treatment, as compared to baseline; and improvements in FEV ₁ , FVC, symptom scores and reduction in exacerbations and rescue salbutamol use	[32]

AQLQ: Asthma Quality of Life Questionnaire; b.i.d.: Twice daily; CFC: Chlorofluorocarbon; DB: Double-blind; EB: Evaluator-blind; F/BDP: Formoterol/beclomethasone dipropionate; F/FP: Formoterol/fluticasone propionate; F/MF: Formoterol/mometasone furoate; FEV₁: Forced expiratory volume in 1 second; FP: Fluticasone propionate; FVC: Forced vital capacity; HFA: Hydrofluoroalkane; ICS: Inhaled corticosteroid; LABA: Long-acting B₂ agonist; m/e PEFR: Morning/evening PEFR; MEF₂₅: Maximum expiratory flow at 25%; MEF₅₀: Maximum expiratory flow at 50%; MEF₇₅: Maximum expiratory flow at 75%; OL: Open-label; PC: Placebo-controlled; PEFR: Peak expiratory flow rate; PG: Parallel-group; pMDI: Pressurized metered dose inhaler; R: Randomized; SAL: Salmeterol; SFC: Salmeterol/fluticasone combination.

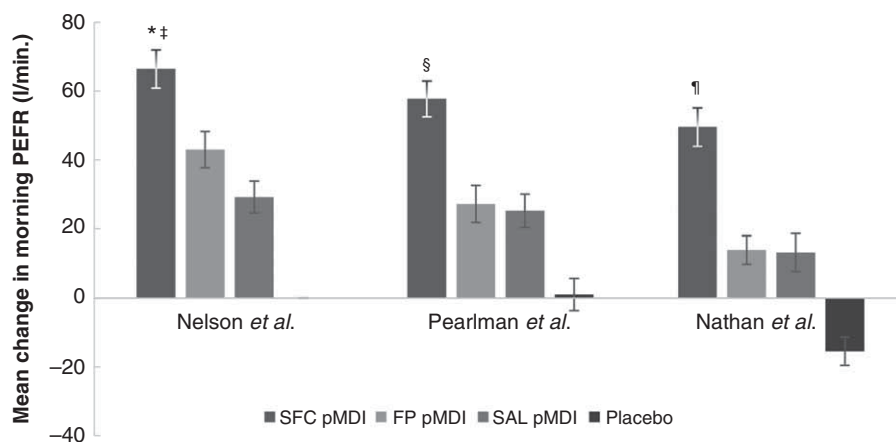


Figure 2. Mean change in morning PEF (l/min) from baseline to week 12 from three studies.

Data taken from [24-26].

* $p \leq 0.028$, SFC versus FP.

† $p < 0.001$, SFC versus SAL.

§ $p \leq 0.0006$, SFC versus FP, SAL and placebo.

¶ $p < 0.0001$, SFC versus FP, SAL and placebo.

FP: Fluticasone propionate; HFA: Hydrofluoroalkane; PEF: Peak expiratory flow rate; pMDI: Pressurized metered dose inhaler; SAL: Salmeterol; SFC: Salmeterol/fluticasone combination.

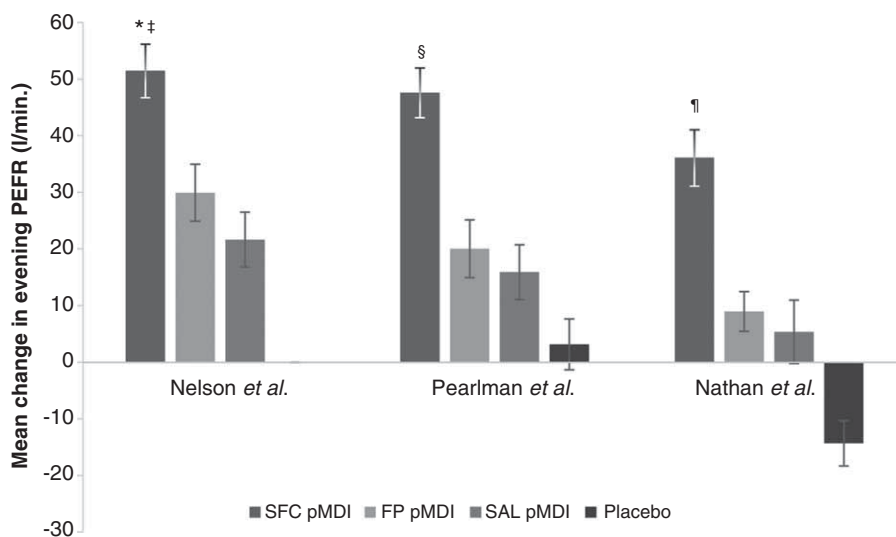


Figure 3. Mean change in evening PEF (l/min) from baseline to week 12 from three studies.

Data taken from [24-26].

* $p \leq 0.028$, SFC versus FP.

† $p < 0.001$, SFC versus SAL.

§ $p \leq 0.0006$, SFC versus FP, SAL and placebo.

¶ $p < 0.0001$, SFC versus FP, SAL and placebo.

FP: Fluticasone propionate; HFA: Hydrofluoroalkane; PEF: Peak expiratory flow rate; pMDI: Pressurized metered dose inhaler; SAL: Salmeterol; SFC: Salmeterol/fluticasone combination.

symptom scores at the end 52 weeks from baseline [29]. A difference of 0.15 ($p = 0.122$) was observed between the SFC pMDI and the F/FP pMDI in the mean asthma symptom scores at week 12 from baseline in a comparison study conducted by Bodzenta *et al.* [28].

3.3 Percentage of days with no asthma symptoms and percentage of nights with no awakenings

Patients reported an increase in the percentage of days with no asthma symptoms and decrease in the percentage of nights with awakenings due to asthma symptoms throughout the

treatment period in several studies evaluating the SFC pMDI. There were a significantly greater percentage of days with no asthma symptoms after treatment with the SFC pMDI (mean change of 26.7% from baseline at week 12; $p < 0.001$), and improvements in the mean change in percentage nights with no awakenings, after treatment with the SFC pMDI (9.0%), were recorded [25]. Greater improvements were observed in the SFC pMDI group in the two other studies as well [24,26]. In one of the studies, the mean number of night-time awakenings reduced in patients treated with the SFC pMDI (-0.04) [24], and in another study, the mean percentage of nights with no awakenings reduced by 19.6% in the SFC pMDI group [26]. A 4.3-fold increase in the proportion of asthma-free days and nights was observed with a daily dose of SFC pMDI 50/250 μg , and a 3.4-fold increase with 50/500 μg , at the end of week 52 from baseline [29].

3.4 Reduction in the use of rescue medication

Studies have reported that the patients treated with the SFC pMDI had a reduced use of rescue medication at the end of the treatment period, as compared with baseline. One of the studies showed that at the end of 12 weeks of treatment, the SFC pMDI group had a significantly greater reduction in the need for rescue salbutamol (-2.1 inhalations/day), as compared with FP and SAL (-0.4 and -0.8 inhalations/day, respectively; $p \leq 0.002$) [25]. Another study showed that the patients who received the SFC pMDI showed significantly higher proportion of days with no rescue salbutamol use (mean change of 32.5%), compared with FP alone (mean change of 13.1%; $p \leq 0.0005$) from baseline to the end of week 12 [24]. Similar results were seen in another study in which the mean percentage of rescue-free days was reported to be significantly greater with the SFC pMDI (61%; $p = 0.028$) than for FP (44%), at the end of the 12-week treatment [26]. Maspero *et al.* reported an increase in the proportions of days and nights free of rescue salbutamol use by 65% with a daily dose of SFC pMDI 50/250 μg and 100% with 50/500 μg , at week 52 from baseline [29]. Another study reported that the mean percentage of rescue-free days ranged between 75 and 79% at 4 weeks and 79 to 83% at 52 weeks from baseline [27].

3.5 Patient satisfaction and quality of life

Sheth *et al.* in 2006 evaluated the performance of the SFC pMDI (50/250 $\mu\text{g}/\text{day}$) with a dose counter in patients with asthma/chronic obstructive pulmonary disease (COPD) using a patient satisfaction questionnaire at baseline and end of study (~ 30 days after the initiation of the pMDI, to allow completion of all labeled actuations) [30]. At the endpoint, 95% of patients were satisfied with the pMDI with a counter, based on ease of use and convenience, and agreed that the counter would let them know when to refill their medication. Also, 73% of patients reported that a pMDI with a counter would help them improve control over their disease [30]. Edin *et al.* published an analysis of results from two studies reporting the Asthma Quality of Life Questionnaire (AQLQ)

scores in patients administered a daily dose of SFC pMDI 42/88 μg (ex-actuated) and 42/220 μg (ex-actuated). Statistically significant ($p \leq 0.006$) and clinically meaningful (≥ 0.5) differences were reported in overall AQLQ scores in both the studies at week 12 [31]. In another study, the AQLQ scores improved numerically in patients receiving the SFC pMDI at 12 weeks of treatment [28]. The same study also reported that 91% assessed the SFC pMDI as good or very good [28].

4. Salmeterol/fluticasone pMDI versus salmeterol/fluticasone multi-dose DPI in asthma

A study conducted by Bateman *et al.* compared the efficacy and safety of SFC 25/50 μg administered as two actuations twice daily via an HFA pMDI versus SFC 50/100 μg , one inhalation b.i.d. via a Diskus (multi-dose DPI), in patients with mild-to-moderate asthma for 12 weeks [32]. It was observed that the SFC pMDI was clinically equivalent to the SFC via Diskus in increasing the mean morning PEFR over weeks 1 – 12 (adjusted mean increases, 43 and 46 l/min; treatment difference, 3 l/min; 95% CI: -6 to 11 l/min) [32]. The results from this study are shown in Figure 4.

Similar results were shown by You-Ning *et al.* in 125 patients administered the SFC pMDI (25/125 μg , two inhalations, b.i.d.) and 123 patients on the SFC via Diskus (50/250 μg , one inhalation, b.i.d.) [33]. At the end and during the 4-week treatment period, there was no significant difference between the SFC pMDI and Diskus groups in morning PEFR (primary efficacy endpoint) and secondary endpoints, including evening PEFR, FEV₁, daytime and night-time symptom scores, and rescue salbutamol use [33]. Another 12-week, double-blind, parallel-group study comparing the SFC pMDI with the SFC Diskus showed that the improvement in mean mPEFR from baseline to week 12 was equivalent in the SFC pMDI and Diskus groups ($n = 509$). Similar improvements in the two groups were also observed in median percentages of symptom-free days and nights and rescue salbutamol-free days and nights from baseline to week 12; the exception was that the median percentage of rescue salbutamol-free nights was significantly greater in the SFC pMDI group at week 1 [34].

5. Safety

5.1 Safety of LABA and ICS as a class in asthma

β -agonists have been associated with cardiac adverse effects (increased heart rate, palpitations and alterations in QTc interval), tremors and decreased serum potassium levels [35]. These side effects are rare with the inhaled route and the currently approved and prescribed doses [35]. In asthma, LABA monotherapy is associated with increased risk of mortality, with the Salmeterol Nationwide Surveillance Study reporting a threefold (non-significant) increase in the risk of death in subjects treated with salmeterol as compared with salbutamol [36],

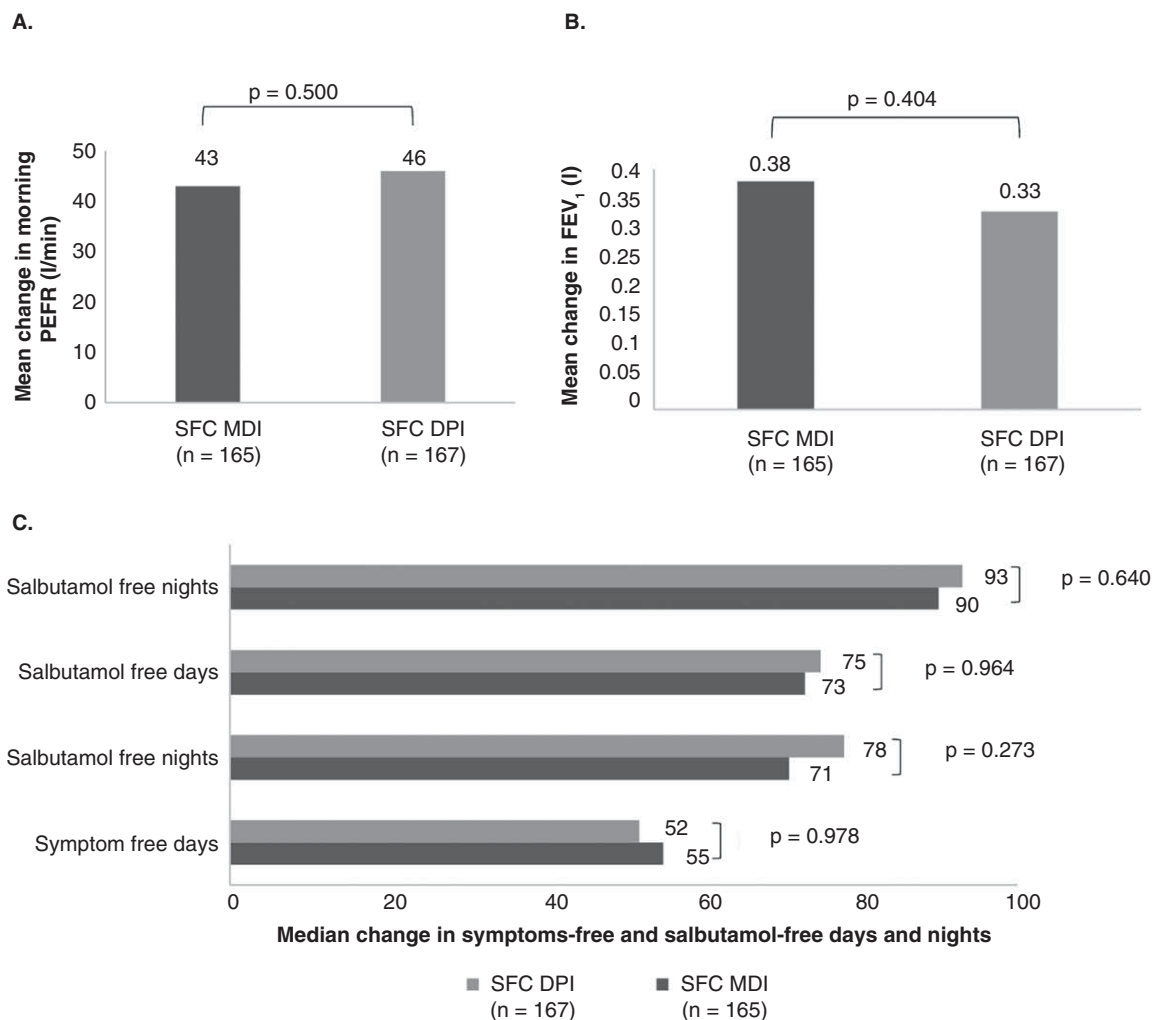


Figure 4. Results from the study by Bateman *et al.*, comparing the SFC MDI with the SFC delivered via Diskus; **A)** Mean change in morning PEF (l/min); **B)** Mean change in FEV₁ (L); and, **C)** Median change in symptom-free and salbutamol-free days and nights from baseline to week 12.

Data taken from [32].

FEV₁: Forced expiratory volume in 1 second; MDI: Metered dose inhaler; PEF: Peak expiratory flow rate; SFC: Salmeterol/fluticasone combination.

and Salmeterol Multicentre Asthma Research Trial (SMART) reporting a fourfold (statistically significant) increase in asthma mortality with SAL as compared with placebo [37]. The subgroup analyses of SMART reported that there was no increase in the risk of asthma mortality when SAL was administered concomitantly with ICS [37]. A meta-analysis of 215 studies with 106,575 randomized subjects and 39,006 patient-years of treatment supported these results, by reporting that there were a total of 35 deaths due to asthma with the use of a LABA alone [38]. The analysis also observed that 48,715 subjects from 127 studies, receiving ICS along with SAL, the deaths due to asthma reduced to nine. Additionally, in 63 studies with 22,600 subjects, no deaths from asthma were reported in whom salmeterol/fluticasone was administered as a combination inhaler [38]. Furthermore, it has been reported that regular ICS therapy provides significant protection against the

risk of mortality [39]. The FDA recommends that LABA monotherapy in patients of all ages with asthma is contraindicated, and that all patients with asthma receive ICS concomitantly when prescribed a LABA – preferably in a single inhaler [40].

Long-term use of ICS has been associated with local and systemic side effects. Local side effects include dysphonia, oropharyngeal candidiasis and cough, and systemic side effects include hypothalamic-pituitary-adrenal (HPA) axis suppression, adrenal suppression, reduction in bone mass, osteoporosis, cataract, glaucoma, increased diabetes mellitus and decreased glucose control [39,41]. Studies indicate that these side effects are increased with oral/systemic administration, as compared with the inhaled route. The side effects also depend on the patients' individual response to the ICS [39]. ICS have been the preferred treatment option for optimal

management of asthma as they improve hyperresponsiveness, and addition of a LABA is the next step in treatment as they improve lung function [15,42]. A combination of LABA and ICS is suggested to work in synergy and decrease airway inflammation and cause bronchodilation [42].

5.2 Safety of salmeterol/fluticasone pMDI in asthma

Overall, treatment with the SFC pMDI was well tolerated in the studies reviewed for this article [24-34]. The most commonly reported adverse events in the studies ($\geq 2\%$ patients), which could be possibly drug-related, were upper respiratory tract infections/inflammation, headache, dysphonia (hoarseness), throat irritation, and cough [24-34].

Oral candidiasis and oropharyngeal plaques were reported infrequently in the studies [24,26,27]. It is known that the long-term use of ICS may cause HPA axis suppression, leading to low plasma levels of cortisol and reduced urinary cortisol excretion [43]. No significant difference was observed in plasma cortisol concentrations when the SFC pMDI was compared with FP and SAL given in two separate inhalers, in a 12-week study [24]. In a tolerability study by Cowie *et al.*, the incidence of abnormalities in urinary cortisol was low for three groups given the SFC pMDI (two inhalations b.i.d. of SFC 25/50, 25/125 or 25/250 μg), from baseline to week 52 [27]. In three separate studies, no clinically relevant differences were noted in the SFC pMDI group with respect to clinical laboratory test data, and no clinically significant unfavorable changes from baseline in 12-lead electrocardiograms were observed after 12 weeks [25,26,28].

Two studies were conducted to compare the SFC pMDI with the F/MF pMDI [29,44]. In one of the studies, Kosoglou *et al.* observed that treatment with the F/MF pMDI (5/200 μg , two inhalations b.i.d.) and the SFC pMDI (21/230 μg , two inhalations b.i.d.) led to comparable reductions from baseline in plasma cortisol $\text{AUC}_{0-24\text{ h}}$ at the end of week 6 [44]. Maspero *et al.* reported a non-significant reduction in plasma cortisol 24-h area under the curve ($\text{AUC}_{0-24\text{ h}}$) with the SFC pMDI 25/125 μg (two inhalations b.i.d.), as against a sustained significant ($p \leq 0.43$) reduction in the F/MF pMDI groups (two inhalations b.i.d. of F/MF 5/100 and 5/200 μg), from baseline at the end of week 52 [29]. Mean change from baseline in the 12-h overnight urinary cortisol/creatinine ratio was observed to be comparable in the SFC pMDI and F/BDP pMDI groups, at the end of week 12 [45]. Another 12-week study comparing the SFC pMDI and the F/FP pMDI reported no systemic effects (e.g., elevation of serum glucose or reduced serum potassium concentrations) due to the use of LABAs [28]. At week 12, no significant difference was observed between the SFC pMDI and SFC Diskus groups in serum cortisol levels from baseline [32].

6. Conclusions

As per the studies reviewed and discussed in this article, it was concluded that pMDIs are efficacious for the long-term

management of asthma. Fixed-dose combinations of salmeterol/fluticasone, F/FP, formoterol/beclometasone and F/MF improve lung function and the QoL, and are well tolerated by patients. There is no difference observed in the efficacy and tolerability of pMDIs as compared to Diskus or SFC. One limitation of the review is the discussion of studies, which use different measures of symptoms; enroll different severity populations of asthma. Further studies in this area would add immense value. The authors believe that the salmeterol/fluticasone pMDI can be considered as the choice of delivery system in asthma patients, considering the key advantages of uniform dose content per actuation, simple and consistent inhalation technique for different types of pMDIs, resistance to pathogens and humidity, portability and cost-effectiveness in long-term use. These factors may contribute to the overall treatment adherence in patients with asthma.

7. Expert opinion

The first commercial pMDI containing isoprenaline came into existence in the year 1956 in the form of the Medihaler-IsoTM by 3M Pharmaceuticals [1]. The evolution and ongoing development for over 50 years now has increased the popularity of the pMDIs among clinicians and patients, most significantly influenced by the factors of convenience, portability and low cost [1,2]. A review of studies on pMDIs has concluded that efficacy and safety of HFA pMDIs is clinically equivalent to CFC pMDIs and at much lower doses [46]. The results also observed that the performance of the now decade-old HFA pMDIs was superior to that of the conventionally used CFC pMDIs [46]. The pMDI is compact, portable, robust, convenient to use and unobtrusive and these attributes give it superiority over a nebulizer. A pMDI can deliver multiple doses at any given time, with a shorter treatment time. It is easy to prepare for treatment as compared with nebulizers, requires lower doses and is relatively inexpensive [47]. When compared with the DPI, the pMDI ensures dose content uniformity. The dose inhaled in a DPI is dependent on particle de-agglomeration, which, in turn, is influenced by the inspiratory flow rate generated by the patient, whereas, in a pMDI, the dose is metered and released as an aerosol, independent of the patient's inspiratory flow [1,47]. Moreover, the content in the pMDI is filled under high pressure and sealed to provide protection against moisture and pathogens [47].

Comparing the deposition of the pMDI with a DPI, $\sim 50\%$ of the largest dose is delivered to the alveolar airways with a pMDI and $\sim 70\%$ of the largest dose of a DPI is delivered to the throat [48]. The incorrect inhaler technique can lead to poor adherence to inhalation therapy [15,49]. Other contributing factors to poor adherence include difficulties in using inhaler devices, using different types of inhalers, misunderstanding instructions and cost [15]. A key advantage of using a pMDI over a DPI is that nearly all pMDIs have the same handling and inhalation technique (press and breathe),

whereas the commercially available DPIs are, generally, difficult to use, requiring different preparation techniques such as loading of a capsule, piercing a blister, moving a lever, or holding the device in a particular orientation [47]. As each DPI device requires a specific set of operating techniques, the patient needs to be trained every time a new device is prescribed [47]. Melani *et al.* in their study including 1664 patients with airway diseases (42% with asthma), of whom 843 used the pMDI and 1,113 used a DPI, reported that the percentages of patients who made at least one critical error with the use of a device were distributed as 12% with the pMDI, 35% with the Diskus and Handihaler, and 44% with the Turbohaler. It was reported that inhaler misuse significantly increased the risk of hospitalization, emergency room visits and courses of oral steroids [13].

Another point to ponder is that all patients after being diagnosed with asthma will have a pMDI prescribed, as rescue medication across the world is predominantly available as a pMDI – intuitively prescribing a pMDI as maintenance therapy will potentially reduce the chances of errors due to switching of devices and remembering steps in using different rescue and maintenance treatment devices and, thereby, enhance patient compliance with the treatment. This is supported by evidence in the literature. When a cohort of patients receiving the SFC via a pMDI were compared with the patients receiving it via a DPI, it was observed that asthma control was better in the outcome year in the pMDI cohort, with reduced frequency of exacerbations, and the treatment success was significantly greater [6].

An important error in using a pMDI is poor actuation-inhalation coordination, which is a critical technique for better lung deposition. This can be especially observed with very young and elderly patients [1,47]. This incoordination can be eliminated by the use of add-on devices such as spacers, also called holding chambers [2]. A spacer creates additional room between the mouth of the patient and the pMDI allowing the aerosol plume to develop. Smaller particles are held in suspension whereas the larger particles precipitate out and these factors all lead to better lung deposition, and reduced oropharyngeal deposition and thereby the local side effects. The spacers also reduce the cold freon effect, generally observed because of the incorrect technique with the use of a pMDI [1,2]. A pMDI used with a non-electrostatic spacer leads to ~ 40% of lung deposition and minimal

oropharyngeal deposition, as compared with < 20% of lung deposition and ~ 70% of oropharyngeal deposition with a DPI [7]. The GINA guidelines on asthma management recommend that a pMDI with a valved spacer (with or without a facemask for infants and children) is the preferred delivery system for adults and children with asthma [15].

Apart from their effectiveness and drug delivery, the integration of dose indicators or dose counters has also increased the treatment adherence of the patients. Dose indicators prevent the patients from underusing or overusing their pMDIs. This is beneficial when a patient requires a reliever medication at the time of an exacerbation. In the absence of a dose counter, the patients relied on misleading and inaccurate measures such as shaking, spray testing or floating the pMDI in water, feeling the weight of the pMDI, or watching the plume in order to check whether their pMDI was depleted of medication. An integrated dose counter/indicator allows the patients to know how many doses are left in the pMDI and alerts them to when their pMDI is running out, and this allows sufficient time to obtain a new one [50].

Further, pMDIs are not only beneficial in asthma but also in COPD. Patients, especially with moderate and severe airway obstruction, have difficulty in generating the required inspiratory flow rate to inhale through a DPI device [51]. This is also an area that can be explored to maximize outcomes and adherence in patients with COPD.

To sum up, pMDIs are clinically effective and may be regarded as the most cost-effective delivery option in patients with asthma. Although there is on-going development in this area (the latest being breath-actuated pMDIs), the HFA pMDI with a dose counter/indicator, along with a spacer, should be the preferred choice for better outcomes and compliance in patients with asthma.

Declaration of interest

N Mehta, B Aggarwal and J Gogtay are employees of Cipla. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. This includes consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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