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EVIDENCE-BASED REVIEW

The dose–response characteristics of inhaled corticosteroids when used to treat asthma: An overview of Cochrane systematic reviews ☆

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Summary Inhaled corticosteroids form the cornerstone of treatment for most patients with asthma. A range of compounds are available with a wide range of prescribable doses. In this overview, we summarize the findings from a number of Cochrane systematic reviews that have examined the relative benefits of different doses of beclometasone dipropionate, budesonide and fluticasone propionate when used to treat children and adults. The key findings are that all inhaled corticosteroids demonstrate a dose–response relationship for efficacy measures, but most of the benefit in mild-to-moderate severity disease is gained in the low-to-moderate dose range of each drug. In this group, high doses of fluticasone lead to small improvements in measures of control at the expense of a steep increase in the incidence of oral side-effects. In patients with severe disease who are dependent on oral steroids, there may be appreciable benefit in reducing oral steroids from very high compared with high doses of fluticasone.

Introduction

During the past three decades, a range of potent synthetic inhaled corticosteroids (ICS) have been developed for the treatment of asthma, including beclometasone dipropionate (BDP), budesonide (BUD) and fluticasone propionate (FP). ICS have an established position in the management of asthma in children and adults. They reduce morbidity and mortality,[1] and are recommended

☆ Please see reference list for Cochrane reviews cited in this evidence-based review.

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in all recent national and international asthma management guidelines.[2,3] Three systematic reviews undertaken using the Cochrane methodology have shown unequivocally that BDP, BUD and FP all lead to significant improvements in airway function, as measured by forced expired volume in 1 s (FEV_1) and peak expiratory flow (PEF); a reduced likelihood of asthma exacerbation; improvement in symptoms; and a reduced need for rescue beta-2 agonist when any daily dose is compared with placebo.[4–6] Although these reviews have allowed a quantitative assessment for outcome measures related to asthma, they cannot provide clear insights into the relative effects of different doses because the trials did not randomize participants to different doses of ICS. Current asthma management guidelines have been developed on the basis of two key assumptions. First, that a dose-related difference in effect may be anticipated (i.e. that a dose–response phenomenon is shown for ICS). Therefore, patients with more severe symptoms or poorer lung function (i.e. poorer control), may benefit from higher doses. Second, that patients with more severe underlying disease as measured by baseline lung function or other markers of control, such as frequency of symptoms, may benefit from higher doses compared with patients with less severe disease. These questions are best addressed by randomized-controlled trials (RCTs), in which participants are allocated to groups in which they receive one of two or more daily doses of an ICS using the same delivery system. In this paper, we examine the evidence presented in a set of Cochrane systematic reviews of such studies.

Cochrane systematic reviews of interest

Four Cochrane systematic reviews addressing the issue of ICS dose response in asthma have been published: (1) inhaled beclometasone at different doses for chronic asthma first published in 1999;[7] (2) inhaled BUD at different doses for chronic asthma first published in 1999;[8] (3) inhaled fluticasone at different doses for chronic asthma first published in 2000;[9] (4) high dose vs. low-dose ICS as initial starting dose for asthma in adults and children first published in 2003.[10] In those trials, the patients with stable asthma were randomized either to high dose (with subsequent step down to lower dose) or maintained on low or medium dose. Henceforth, reviews one to three will be termed the dose–response reviews, and the fourth review will be termed the starting-dose review.

Review methodology

Objectives

Each of the dose–response reviews had the primary objective of assessing whether BDP, BUD and FP had a dose–response effect for outcomes related to efficacy and side-effects. The primary objective of the starting-dose review was to establish whether patients starting an ICS for asthma control gained benefits that were dose related (i.e. to establish the optimal starting dose of ICS in ICS-naïve participants). Both the dose–response reviews and the starting-dose review considered all outcome measures, except those concerned with growth and bone turnover.

Study inclusion criteria

In the dose–response reviews, the studies had to have a treatment arm of BDP, BUD or FP compared with the same ICS at a different dose. The studies also had to meet the following criteria: (1) have recruited patients with chronic asthma over the age of 2 years; (2) be RCTs of parallel group or crossover design; (3) involve treatment administered using a hand-held inhaler device; and (4) have a treatment period of 1 week or longer. Trials including patients under the age of 2 years or using a nebulizer were specifically excluded. The inclusion criteria for the starting-dose review differed from that of the dose–response reviews in a number of important respects. Participants were not permitted to use an ICS for at least 1 month before randomization, and the duration of treatment was a minimum of 4 weeks.

Comparisons

In the dose–response reviews, dose comparisons were not specified a priori. In the BDP and BUD dose–response reviews, results were reported according to the fold difference in daily dose of ICS. In the FP dose–response reviews, dose comparisons were made on the basis of the total daily dose of FP. The authors did, however, arbitrarily define dose ranges to aid the description of their findings. These ranges were low-dose range ($\leqslant$200 mcg/d), moderate-dose range (400–500 mcg/d), high-dose range (800–1000 mcg/d) and very high-dose range ($>$1000 mcg/d). In the starting-dose review, a priori-defined dose range comparisons were made. It is important to appreciate that these dose ranges differ from those described in the dose–response reviews. In particular, separate dose ranges were

Table 1 Dose range comparison groups (mcg/day) for the starting dose review.

	BDP/BUD		FP	
	Child	Adult	Child	Adult
Low dose	<200	<400	<100	<200
Moderate dose	200 to 400	400 to 800	100 to 200	200 to 400
High dose	>400	>800	>200	>400

BDP, beclometasone dipropionate; BUD, budesonide; FP, fluticasone proprionate.

defined for adults and children. These are detailed in Table 1. In the starting-dose review, studies assessing different ICSs were pooled according to the pre-defined dose ranges. In the starting-dose review, studies designed to compare a step down dose approach to a fixed ICS dose were analyzed separately. For each of the dose–response reviews, subgroup analyses based upon asthma severity were planned. In order to do this, trials had to be categorized according to severity. The 1995 consensus guidelines developed by the global initiative for asthma (GINA) provide bandings for disease severity. These are based on degrees of symptom control that apply to patients before starting treatment or the amount of treatment required to provide adequate control.[11] An attempt was made in these reviews to retrospectively categorize the included studies according to the GINA bandings. In the dose–response reviews, studies were categorized on the basis of the presence or absence of regular oral corticosteroid (OCS) use at enrolment, and were analyzed separately.

Results

Is there evidence for an inhaled corticosteroid dose response?

In the BDP dose–response reviews, individual trials evaluated a wide range of comparisons spanning differences in dose from less than two-fold to five-fold. Most of these trials were crossover studies with small patient numbers, and almost all assessed different daily dose combinations of BDP and could not be pooled in a meta-analysis. For most outcomes, no significant differences between doses were found. Insufficient data were available to make a reliable assessment of asthma severity. A meta-analysis including the data from two parallel-design studies, which compared BDP 800 mcg/d with BDP 400 mcg/d, found statistically significant but small improvements in measures of airway function favouring the higher dose.[12,13] These included improvements in morning PEF, weighted mean difference (WMD) 11 L/min 95% confidence intervals (95% CI) 4–19 L/min and evening PEF, WMD 8 L/min (95% CI 0–16 L/min). No statistical heterogeneity was apparent when the results of these studies were pooled, but it is important to appreciate that the trials did differ in a number of important respects. These include the fact that, in one study, an aerosol metered dose inhaler was used for the lower dose, whereas a dry powder inhaler was used for the higher dose.[12] The studies also had widely differing durations: 6 weeks[12] to 12 months.[13]

Mild to moderate asthma in patients not treated with oral corticosteroids

Most studies in the BUD dose–response reviews that recruited patients not receiving OCSs at enrolment were judged to have included patients with mild-to-moderate asthma. Differences in trial design, outcomes reported and limited data availability meant that a meta-analysis was not possible. In the case of the FP dose–response reviews, most of the participants included in studies in which OCS use was an exclusion criterion were judged to have mild-to-moderate asthma. Four trials included participants with mild-to-moderate asthma,[14–17] 11 with moderate asthma,[18–28] one with mild, moderate and severe asthma[29] and one with moderate to severe asthma.[30] A meta-analysis of outcomes reported in the trials comparing FP at different dose was undertaken. The results are summarized in Table 2. The data for FEV_1 are presented graphically in Fig. 1. No studies were included in non-OCS treated patients that included a very high dose FP (>1000 mcg/d) treatment arm. Minimal data were available for comparisons of moderate dose (400–500 mcg/d) compared with high-dose FP (800–1000 mcg/d). For comparisons over the low and moderate dose range (100 vs. 200 mcg/d, 100 vs. 400–500 mcg/d and

Table 2 Relative efficacy of higher compared with lower dose fluticasone in participants not treated with oral steroids.

Dose comparison (mcg/d)	Δ FEV_1 (L)*		Δ morning PEF (L/min)*		Δ evening PEF (L/min)*		Δ daily asthma symptom score*		Δ night-time awakening score*		Δ daily use rescue beta-2 agonist (puffs/d)*		Withdrawal due to lack of efficacy	
	WMD (95% CI)		WMD (95% CI)		WMD (95% CI)		SMD (95% CI)		SMD (95% CI)		WMD (95% CI)		RR (95% CI)	
	n	*N*	*n*	*N*	*n*	*N*	*n*	*N*	*n*	*N*	*n*	*N*	*n*	*N*
Outcome (difference between higher dose and lower dose fluticasone)														
50 vs. 200	0.04 (−0.08 to 0.16)		7 (−2 to 17)		8 (−1 to 17)		−0.32† (−0.10 to −0.54)		−0.09‡ (−0.02 to −0.16)		0.1 (−0.4 to 0.5)		1.32 (0.91 to 1.91)	
	2	313	2	313	2	313	2	313	2	313	2	313	2	313
100 vs. 200	0.0 (−0.04 to 0.05)		6† (2 to 10)		6‡ (2 to 11)		0.04 (−0.07 to 0.15)		−0.17† (−0.04 to −0.30)		0.14 (−0.1 to 0.37)		1.0§ (0.81 to 1.26)	
	8	1238	10	1670	6	999	8	1252	6	921	9	1409	7	1190
200 vs. 400–500	0.03 (−0.04 to 0.10)		8† (4 to 12)		9† (5 to 13)		0.06 (−0.02 to 0.13)		—		0.18 (−0.14 to 0.51)		1.33 (0.94 to 1.89)	
	5	740	8	1731	4	1150	4	580			4	580	4	697
100 vs. 400–500	0.01 (−0.09 to 0.10)		8‡ (1 to 15)		—		0.31‡ (0.03 to 0.6)		—		—		—	
	3	351	3	593		2	194							
200 vs. 800–1000	0.13† (0.03 to 0.24)		8† (2 to 15)		8‡ (1 to 15)		0.02 (−0.07 to 0.11)		—		0.11 (−0.29 to 0.50)		1.24 (0.72 to 2.15)	
	2	291	4	763	2	424	2	291			2	291	3	448

FEV_1, forced expired volume in 1 s; FP, fluticasone proprionate; *n* = total number of trials contributing to analysis; *N* = total number of patients contributing to analysis; PEF, peak expiratory flow; RR, relative risk; SMD, standardized mean difference; WMD, weighted mean difference; 95% CI, 95% confidence interval; *, change compared to baseline. ‡$P<0.05$; †$P<0.01$; § significant heterogeneity between studies, $P<0.05$; — no studies.

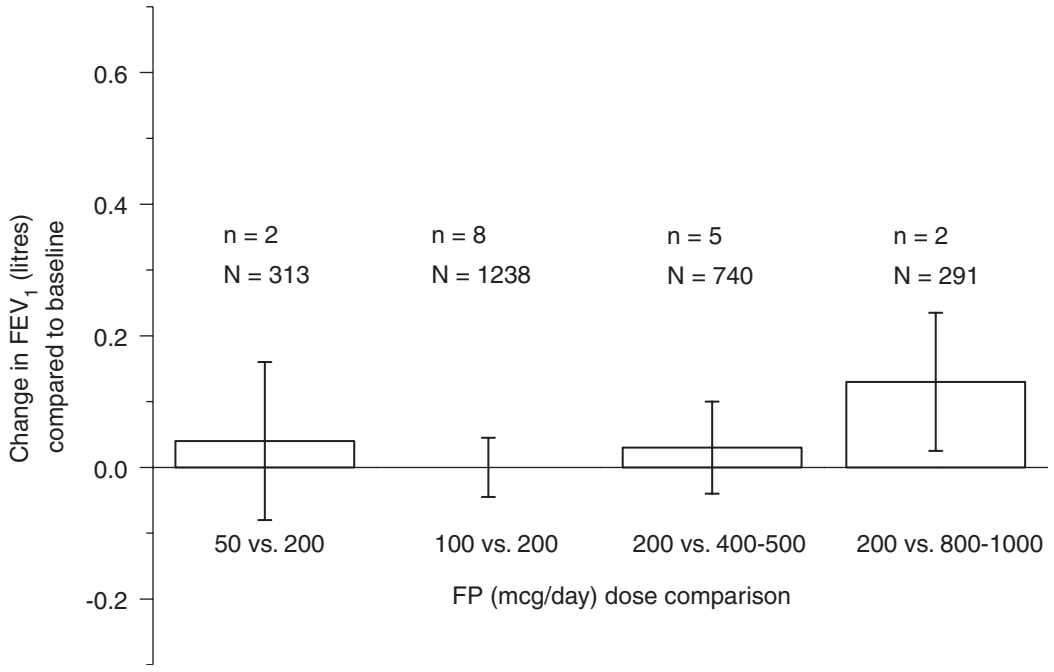

Figure 1 The effects of fluticasone propionate compared at different dose on FEV_1 in mild to moderate asthma.[9] The data are individual meta-analyses undertaken for studies that compared fluticasone propionate at each dose comparison. FP, fluticasone propionate; *n*, number of studies contributing to meta-analysis, *N*, total number of participants included in the meta-analysis. The error bars are 95% confidence intervals.

200 vs. 400–500 mcg/d), no dose–response effect was apparent for FEV_1. However, a statistically significant effect was seen when high-dose FP (800–1000 mcg/d) was compared with low-dose range FP (200 mcg/d), although the additional benefit was relatively small. For diary card PEF, a statistically significant dose–response effect was apparent over most parts of the dose range. Comparisons of FP in the low-dose range (100 vs. 200 mcg/d) showed slightly greater improvements in morning and evening PEF with the higher dose. Comparisons between low and moderate dose (100 or 200 mcg/d vs. 400–500 mcg/d), and low (200 mcg/d) compared with high dose (800–1000 mcg/d), showed similar magnitude effects that were greater with the higher dose. By contrast, for symptom scores, significant differences between doses favouring the higher dose were seen in comparisons between low and moderate dose but not for comparisons between the high dose and low-dose ranges. No difference between any dose comparison was seen for rescue beta-2 agonist use.

Moderate-to-severe asthma

Two studies that assessed BUD at different doses reported the number of patients who withdrew because of asthma exacerbation.[31,32] Both were conducted in patients judged to have moderate-to-severe asthma using GINA criteria. No significant difference between treatment groups was apparent for FEV_1 (% predicted), WMD 1.4% (95% CI −0.8 to 3.6%) or morning PEF, WMD 2 L/min (95% CI −13 to 16 L/min). However, a significant reduction in the likelihood of withdrawal due to exacerbation was apparent for BUD 800 mcg/d compared with 200 mcg/d, RR 3.93 (95% CI 1.4–10.9), corresponding to a number needed to treat (NNT) of 33 (95% CI 20–100). This result was influenced strongly by one large high-quality RCT.[32] Another large multicentre study randomized 671 adults with moderate-to-severe asthma to treatment for 6 weeks with either FP 1000 or 2000 mcg/d.[33] A proportion of patients in this trial were receiving OCSs at enrolment. Only evening PEF showed a significantly greater improvement favouring the higher dose of FP: mean difference 7 L/min (95% CI 0–15 L/min). No difference between the two doses was apparent for FEV_1, morning PEF, symptom-free days, or daytime/night-time rescue beta-2 agonist use.

Severe asthma treated by oral corticosteroids

Budesonide. Two studies comparing BUD at different doses were undertaken in patients judged to have suboptimally controlled, severe asthma. In

both, a significant proportion of patients were receiving OCS at the time of enrolment. One was conducted in adults,[34] the second in children.[35] In neither were data presented in a form that allowed inclusion in a meta-analysis. Significant improvements, favouring high-dose BUD over low-dose BUD, were apparent for a number of outcomes in each study. In the adult study, FEV_1 and morning PEF both improved on 1600 mcg/d compared with 200 mcg/d, by 0.13 L ($P<0.05$) and 18 L/min ($P<0.01$), respectively. In the study in children, BUD 800 mcg/d compared with 200 mcg/d produced significantly greater improvements in FEV_1 compared with baseline (4% predicted, $P=0.015$), morning PEF (2.3% predicted, $P<0.001$), and reduction in daily beta agonist use (16%, $P=0.036$). Only one study evaluated the relative oral steroid-sparing efficacy of different doses of BUD.[36] This parallel group study in 159 participants assessed the relative oral prednisolone-sparing efficacy of BUD 1600 vs. 800 mcg/d in adults. Prednisolone dose tapering was undertaken using a forced-down titration approach. No significant differences were apparent between doses for either the percentage reduction in daily prednisolone dose compared with baseline or the number of patients who were able to discontinue prednisolone.

Fluticasone. Two parallel group studies were conducted in patients treated with OCS to test the effect of FP as an OCS-sparing agent.[37,38] Both were large, multicentre trials of good methodological quality conducted in adults with severe asthma. Dependence upon oral prednisolone for asthma control at the time of enrolment was an inclusion criterion for both studies. Two nominal daily doses of FP were compared in each trial: FP 1000 or 2000 mcg/d delivered via the Accuhaler dry powder inhaler in patients receiving prednisolone 13.0–13.6 mg/d, and FP 1500 or 2000 mcg/d delivered via a metered dose inhaler in patients receiving prednisolone 9.5–10.2 mg/d. A high proportion of patients (>80%) in both studies were also receiving treatment with a regular ICS at enrolment. Reduction in daily dose of oral prednisolone was the primary outcome measure in both studies. Both trials were of 16 weeks duration. Criteria for prednisolone dose reduction were established a priori in both trials, and were based around maintenance of stable asthma control in relation to baseline. The results from these studies could be pooled. Significantly more patients were able to discontinue oral steroid therapy with FP 2000 mcg/d compared with FP 1000–1500 mcg/d, NNT 6 (95% CI 3–25). Highest dose FP also resulted in significantly greater reductions in daily oral prednisolone requirement, WMD 2.0 mg/d (95% CI 0.1–4.0 mg/d).

Is there evidence that starting dose is important?

Fixed dose comparison

Symptomatic asthma and suboptimal asthma control were inclusion criteria for many of the studies. Statistically significant but small improvements in FEV_1 were found for high-dose ICS compared with moderate dose ICS, WMD 5.3 (% predicted) (95% CI 0.7–10.0 [% predicted]). No difference in PEF was seen. When moderate and low-dose ICS were compared, significant improvements were observed in morning PEF, WMD 11.1 L/min (95% CI 1.3–20.9 L/min) and nocturnal symptoms, standardized mean difference (SMD) 0.3 (95% CI 0.1–0.5).

Step down approach

Studies in adults incorporating a step down versus constant ICS dose used BUD 800–1600 mcg/d reducing to 200 mcg/d compared with a constant dose of 200–400 mcg/d; studies in infants compared nebulized BUD 2 mg/d reducing to 0.5 mg/d versus 0.5 mg/d. A single study in children used FP 1000 mcg/d reducing to 100 mcg/d versus 200 mcg/d. Pooled analyses, including studies that compared an initial high dose with subsequent step down to a constant moderate/low ICS dose, showed no significant differences in lung function, symptoms, rescue medications or asthma control between the two treatment approaches.

Are side-effects dose-dependent?

Oropharyngeal side-effects

Few of the studies that compared different daily doses of either BDP or BUD in the dose–response reviews reported the incidence of oropharyngeal side-effects. A pooled estimate of relative risk (RR) according to dose could not be calculated. By comparison, side-effects of FP were reported for a wide range of doses. A significantly greater risk of hoarseness/dysphonia was apparent for high-dose FP (800–1000 mcg/d) compared with low-dose FP (50–100 mcg/d) RR 0.14 (95% CI 0.03–0.77). The corresponding number needed to harm for FP at high- compared with low-dose was 25 (95% CI 14–100) for a 4–8 week treatment period. No difference in the likelihood of hoarseness was apparent for dose comparisons over other parts of the dose range. No difference in the incidence of sore throat/pharyngitis or oral candidiasis was apparent for any FP dose comparison.

Hypothalamo-pituitary axis function
Effects of treatment on hypothalamo-pituitary axis (HPA) function were assessed using a number of measures in the dose–response reviews. These included basal measurements of HPA activity (morning plasma cortisol levels, overnight and 24-h urinary cortisol levels), and dynamic tests of adrenocortical reserve (plasma cortisol levels after corticotrophin injection or infusion). Few studies reported these outcomes, and it was not possible to derive a pooled treatment effect across studies.

Discussion

In this overview, we have summarized four systematic reviews that examined the evidence for dose–response effects with BDP, BUD and FP. A proof-of-principle has been shown, in that all three ICS reviewed here have evidence of dose-associated improvements in one or more outcome measures. However, it is important to appreciate that aspects of trial design will influence the likelihood of detecting such effects. For example, small and underpowered individual trials cannot reliably reject the null hypothesis of 'no difference' between treatment arms. Most of the studies assessing BDP and BUD in mild-to-moderate severity asthma were of this type. Furthermore, these studies could not be pooled in a meta-analysis because of a lack of commonality in outcome measurements across trials and inadequate data reporting. The apparent lack of a dose–response in some outcomes may have been the consequence of trial size, consistency of data collection and adequacy of result reporting rather than any intrinsic properties of BDP or BUD. By contrast, studies of higher and low-dose FP often reported the same outcomes, so permitting a more powerful pooled analysis. This revealed a statistically significant dose–response effect for a number of outcomes in patients judged to have asthma of mild-to-moderate severity. However, the dose–response curve seems to be shallow. Statistically significant greater improvements in airway function and symptoms were found when high-dose FP (800–1000 mcg/d) was compared with lower doses (200 mcg/d), but the incremental advantage was small, as shown for the effect on FEV_1 in Fig. 1.

To set these observations into perspective, it is worth considering systematic reviews that compared ICSs at different doses to placebo.[4–6] Significant gains in asthma control were reported with nominal daily doses as low as 200 mcg (BDP or BUD)[4,5] or 100 mcg (FP).[6] With higher doses (seen most clearly in the review of FP vs. placebo),[6] the benefit over placebo seems to be greater with higher doses (Fig. 2). Those trials tested different doses in different study populations, so the analysis in Fig. 2 cannot be used as proof of a dose–response effect—unlike the trials summarized in Fig. 1, in which patients in the same study populations were randomized to receive one or other dose. Taken together, Figs. 1 and 2 suggest very strongly that the greatest proportional gains in control compared with no ICS, occur at the lowest dose, with only modest additional benefits from higher doses. Although the incremental gain in efficacy with higher doses seems to be small, in the case of FP (for which there are adequate data, unlike BDP or BUD), higher doses may be accompanied by increased risk of oropharyngeal side-effects. Paucity of data and data reporting did not allow an overall assessment of the effects of dose on HPA function.

Overall, the systematic reviews reported in this overview support an approach to asthma management that recognizes some variability in control that is dose dependent and recommends dose titration according to measures of control. The British Thoracic Society (BTS/SIGN 2003) guidelines suggest starting with an ICS dose of 400 mcg BDP equivalent per day, and then titrating down to the lowest dose needed to maintain control.[2] Evidence from these reviews support these recommendations. However, the core of patients seem to require higher doses to achieve control. In patients with moderately severe and severe asthma, modest additional reductions in asthma exacerbations and improvement in airway function may be gained from the use of higher rather than lower dose BUD. Data from studies that specifically assessed the OCS sparing properties of FP also suggest that adults can derive clinically worthwhile reductions in the amount of prednisolone required to maintain control if very high doses (2000 mcg/d) are used.

There is now a substantial body of evidence to guide the use of ICSs in asthma. In clinical practice, regular reassessment of ICS dose requirement by the clinician and patient in the context of an asthma management plan should take place. This will allow tailoring of ICS dose to the individual's needs. Trial data will never predict the outcome for an individual patient in clinical practice, but doctors and patients can gain reassurance from the knowledge that most asthmatics will achieve good control in the lower part of the available ICS dose range. Future studies of ICS dose–response should concern long term (>12 months) effects on

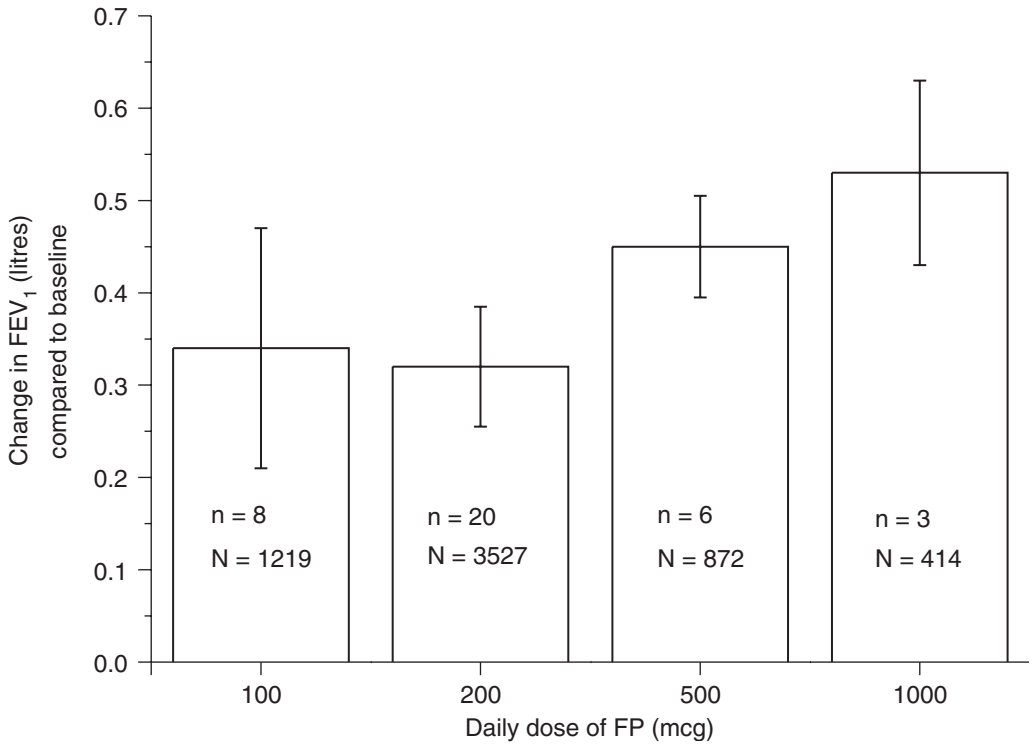

Figure 2 The effect of fluticasone propionate on FEV_1 compared with placebo in mild-to-moderate asthma.[6] The data are pooled meta-analyses undertaken for studies that compared each dose of FP with placebo. *n*, number of studies contributing to meta-analysis; *N*, total number of subjects included in meta-analysis. The error bars are 95% confidence intervals.

health status, exacerbations and mortality in patients with severe asthma. These should be coupled with assessment of adverse outcomes, including suppression of adrenal function, bone turnover and growth in children. These types of prospective studies will need large patient numbers if they are to have sufficient power to detect clinically meaningful differences for such outcomes.

Practice points

- In mild-to-moderate asthma dose-dependent improvements in markers of control occur, but the dose–response profile is shallow and most benefit is gained at low moderate doses.
- In mild-to-moderate asthma, high doses of FP are accompanied by a relatively steep increase in oral side-effects with little improvement in markers of control.
- For patients who require ICS, starting with a moderate dose is as effective as starting with a high dose and stepping down.
- A core of patients with severe asthma, particularly those receiving OCS, will gain benefit from very high dose ICS.

Research directions

- Long-term assessment of the safety characteristics of ICSs, especially in those groups who will accrue the greatest exposure: children and high-dose users.
- Definition of the effects of moderate, high and very high dose ICS in severe asthma on mortality, hospital admissions and health-related quality of life.

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