



Guideline topic: Pharmacological management of asthma
Evidence table 4.22: Combined therapy of inhaled steroids and long acting B2 agonist

Author	Year	Study type	Quality rating	Population	Outcomes measured	Effect size	Confidence intervals / p values	Comments
Bateman ¹	1998	RCT multicentre, double blind, double dummy 2 week run in then 12 weeks treatment Salmeterol/fluticasone 50/100mcg BD in combination inhaler vs concurrent	++	244 patients, 12 to 78 years, symptomatic on ICS BDP 400 – 500/day or fluticasone 200 – 250/day PEFR 50 – 85% after salbutamol No oral steroids within 4 weeks of run in	1) serum cortisol Difference in mean improvement of morning peak flow over 12 weeks 2) Difference in improvement in evening peak flow 3) FEV1 Mean change from baseline % mean change from baseline 4) % patients c symptom scores of zero, daytime and night-time	1) difference –9l/min 33 and 42l/min for concurrent and combination 2) difference –5L/min 36 and 30 l/min (comb vs conc) 3) 0.20 and 0.17l (comb vs conc) Difference –0.03L 6%	1) CI –17,0 Ns difference between treatments p = 0.098 2) CI –13,2 NS difference between treatments p = 0.241 3) CI –0.12, 0.05L no difference 4) NS difference 5) No difference 6) No difference	Mean compliance approx 94% No advantages/disadvantages of combination vs concurrent

					5)side effects and adverse events 6)serum cortisol			
Van den Berg ^{sup}	2000	RCT, multicentre, double blind, double dummy, 9 countries 2 week run in, 12weeks treatment concurrent vs combination of salmeterol/ fluticasone 50/100mcg	++	257 children 4-11years (mean 7.6) symptomatic on ICS BDP 400-500mcg or fluticasone 200-250mcg PEFR >50% and <85% after salbutamol No oral steroids	1)Mean morning peak flow improvement from baseline over 12 weeks 2)mean evening peak flow improvement from baseline 3)FEV1, improvement from baseline at week 12 4)Symptom score and use of salbutamol PRN 5) safety, adverse effects, mean cortisol conc	1) -5L/min) 28l/min vs 33l/min (conc vs comb) 2) -4l/min 25l/min vs 29L/min (conc vs comb) 3) -0.08L 0.13 vs 0.21L	1) CI -10,0l/min P= 0.103 NS 2) CI -9,1L/min P=0.164 NS 3) CI -0.14,-0.01L p= 0.052 NS No difference No difference	No advantages or disadvantages of concurrent vs combination
Chapman ³	1999	Randomised controlled trial, 5 countries double blind, double dummy 28 weeks combination inhaler salmeterol/ fluticasone 50/250mcg	++	371 patients age 13-75 years (mean 42) symptomatic on inhaled corticosteroids BDP 800 to 1200mcg or fluticasone 400-600mcg/day No oral steroids PEFR 50-85%	1)Difference in morning PEFR over 12 weeks (improvement from base) 2) Difference in evening PEFR over 12 weeks 3) symptom free days	Concurrent vs combination 1) -6l/min (36 vs 43l/min) 2) -10l/min (25 vs 35l/min) 3) 0%	CI -13 to 0L/min P=0.114 CI-16 to -4L/min P=0.008 (favouring combination) CI -4 to 0% CI-9% to 0	No exacerbation rate Both treatments showed significant improvement from baseline No advantages/

		BD combination vs concurrent		after salbutamol	(median difference) 4) symptom free nights >5 (median difference) 5) FEV1 at week 28 (difference) 6) salbutamol use 7)safety, side effects and serum cortisol	4) -3% 5) -0.02L/min 6)-3% (mean difference) 7) no significant difference	CI -0.09 to 0.05 CI -6 to 0%	disadvantages of combination vs concurrent
Aubier ⁴	1999	RCT, multicentre, double blind, double dummy 28 weeks Salmeterol/fluticasone (50/500mcg) BD combination vs concurrent vs fluticasone 500 mcg only	++	503 patients 12-79 years (mean 48) symptomatic on ICS BDP 1500-2000mcg/day or fluticasone 750-1000/day No oral steroids PEFR 50-85% after salbutamol	1) difference in morning PEFR over 12 weeks 2) difference in evening PEFR over 12 weeks 3) difference in FEV1 at week 28 4) safety, side effects, serum cortisol and 24 hour urine cortisol	1) -3.1l/min Concurrent vs combination mean improvement 33l/min vs 35l/min 2) -6l/min conc vs comb 3) -0.1 (comb vs conc	1) CI -10 to 4l/min NS difference conc vs comb P<0.001 FP only 2) CI -13 to 1l/min NS difference conc vs combi P<0.001 FP only 3) p=0.061 No significant difference	Concurrent and combination did significantly better for all outcomes compared to fluticasone alone No advantages/disadvantages of combination vs concurrent

1. Bateman E, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. *Clin Drug Invest* 1998;16(3):193-201.
2. Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. *Pediatr Pulmonol* 2000;30(2):97-105.
3. Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J* 1999;6(1):45-51.
4. Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respir Med* 1999;93(12):876-84.