Guideline topic: Pharmacological management of asthma
Evidence table 4.11b: Add-on drugs for inhaled steroids: Long acting or oral B2 agonists

Author	Year	Study type	Quality rating	Population	Outomes measured	Effect size	Confidence intervals / p values	Comments
Adults								
Brambilla[1]	1994	RCT	++	159 patients aged 18-67 (mean 41). FEV, 50-90% pred. And >15% reversibility to b2 agonists. Compared inhaled salmeterol with oral SR terbutaline. Study perios 1 week run in and 2 week treatment.	No. of awakening free nights PEF	50% salmeterol vs 27% terbutaline Salmeterol am PEF 351+/-109 l/min. PEF variation 6+/-% (salmeterol) vs 11+/-12% (terbutaline) Rescue decreased during daytime for salmeterol group	p=0.003 NS in evening PEF. PEF variation reduced in salmeterol group p=0.01 p=0.04 for daytime NS difference in treatment groups at night	Compared to oral SR terbutaline 5mg bd, inhaled salmeterol 50 m g bd causes a minimal increase in am and pm PEF, but did cause a significant improvement in nocturnal asthma control and improved sleep. 66% of patients on salmeterol on inhaled corticosteroids and 11% oral steroil whil in the terbutaline group 67%

								were on ICS 13% oral steroid.
Crompton[2]	1999	RCT	++	118 patients aged 18-67 (mean 41). Nocturnal fall PEF and symptoms on 400 m g-2000m g inhaled or >=20mg oral steroids. Compared bambuterol with inhaled salmeterol. Study period of 8 weeks	Increase in am PEF from baseline. pm PEF, % fall in PEF, No. of night time awakenings, % of nights with no awakening, No. of puffs of rescue medication, asthma symptoms	50 l/min – bambuterol 55 l/min – salmeterol All improved by both treatments	NS differences in treatment with any outcome measures	In this short study, bambuterol 20mg po nocte and salmeterol 50 m g inh bd produced similar improvements in PEFR, nocturnal asthma symptoms and requirement for rescue medication in asthmatics using moderate doses of corticosteroids. Both treatments were well tolerated with similar incidence of tremor, but treatment with bambuterol was significantly cheaper.
Gunn[3]	1995	Crossover RCT	+	152 patients aged 17-78 (mean 54 years) Nocturnal asthma symptoms 3/7	Severity of sleep disturbance (0-3) Increase in PEF Increase in FEV_1	Both treatments reduced scores to <half baseline value. 42 l/min – bambuterol 53 l/min – salbutamol CR	p<0.001 NS between treatments p<0.0001 NS between	Both bambuterol and salbutamol CR improved baselind lung function and

				>=800 µg inhaled corticosteroid (no oral steroids) 15% reversibility to b 2 agonists . Compared bambuterol vs CR salbutamol over 6 weeks	Increase in FVC	0.10L – bambuterol 0.14L – salbutamol CR 0.16L – salbutamol CR	treatments p<0.01 NS between treatments p<0.01NS between streaments	reduced the sevirity of night time symptoms in asthmatics on moderate dose inhaled corticosteroids over this short study time. There was no significant difference in treatments except that bambuterol caused less tremor than salbutamol CR
Ringbaek[4]	1996	Crossover RCT	+	59 patients aged 19-73 (mean 47). Mean FEV, 64%pred. 26.6% reversibility to b 2 agonists. Compared inhaled salmeterol with oral salbutamol CR. Study period 4 wkks and 2 weeks washout.	Increase in am PEF from baseline % days asymptomatic % days free from rescue b 2 agonist use.	35 l/min – salmeterol vs 19 l/min salbutamol 28% salmeterol vs 13% salbutamol 38% salmeterol vs 24% salbutamol	p=0.04 p=0.004 p=0.01	Salmeterol 50 mg bd was more effective than salbutamol CR 8mg po bd at reducing day and night time symptoms and rescue b 2 agonist use. It was also better tolerated. This paper is only available in Danish, making methodological evaluation difficult.
Wallaert[5]	1999	RCT	+	117 patients aged 20-70 (mean age 45). Nocturnal	Increase in am/pm PEF from baseline. Nocturnal and	28 l/min / 20 l/min on bambuterol, 29 l/min, 23 l/min on salmeterol	Bambuterol – p<0.05 Salmeterol –	Bambuterol 20mg po nocte and salmeterol 50 µg inh bd

				fall in PEF and symptoms on 800 m g-2000m g inhaled and/or >=20mg oral steorids per day. Compared oral bambuterol with inhaled salmeterol. Study period of 6 weeks.	daytime symptoms. Rescue inhaled b 2 agonist use.	Nocturnal awakenings reduced in both groups. Consumption of rescue at night was lower in both groups	p<0.001/0.01 p<0.01 Bambuterol – p<0.05 Salmeterol – p<0.001 NS difference between treatments	improved asthma control and nocturnal symptoms to a similar degree with a similar side effect profile.
Children								
Akpinarli[6]	1999	Randomised, placebo-controlled trial and blind	+	32 Asthmatic children (6-14 y) on ICS (400-800 mcg/d) and still symoptomatic. Formoterol 12 mcg or placebo added to ICS for 6 weeks	1] symptom scores (0-9), composite of day/night cough, wheeze and shortness of breath. 2] beta 2 agonist use per week 3] FEV1 am/pm PEFR 4] PC20	Compared to baseline Formoterol reduced score-3 Placebo reduced score 0 Formoterol reduced beta 2 agonist use by –3 and placebo by 0 FEV1 (formoterol) + 3 Am PEFR 19 Formoterol 0.05	95% ci-7 to-2 95%ci-1 to 1 P<0.05 95%ci-6 to –2 95%ci-2 to 2 P<0.05 95%ci-23 to 29) 95%ci 2 to 181 p<0.05 95%ci 0.57 to 0.74 NS	Formoterol reduced asthma symptoms and beta agonist use, increased PEFR 95% ci related to 6 weeks compared with base line. P-values relate to comparison between formoterol and placebo No adverse effects seen
Verberne[7]	1998	Double-blind, randomised, placebo controlled	++	177 asthma children (6-16y), mild to moderate, currently on	1] symptoms dyspnoea (0,1,2,3) am/pm wheeze (0,1,2,3)am/pm	% children no symptoms during a 2 week period:BDP400+Salm 34%, BDP800 39% and BDP400+placebo 35%	1) NS, at no time point were there sign, differences	Found no additional benefit of adding salmeterol to

				BDP 400 mcg /d Study treatment was placebo or BDP 800 mcg/d or salmeterol 100mcg/d over a 12 month period	cough(0,1,2,3)am/pm 2) rescue med. Use (pred. Courses) 3) lung function PEFR FEV1 PD20	3) BDP400+salm slightly better PEFR in first months change FEV1(BDP400+salm)=4.3% (BDP800)=5.8% (BDP400+placebo)=4.3% No significant differenct between groups, all groups increased PD 20 compared to baseline	in symptom scores 2) NS Compared to baseline 95%ci (1.3, 7.2) 95%ci (2.9, 8.7) 95%ci (2.1, 1.3) NB. Between groups NS	BDP 400 compared with adding placebo or doubling the dose of BDP. At end of study, after stopping Salmeterol group noted a reduction in FEV1, this did not occur in other groups. Growth was significantly slower in BDP800 group.
Byrnes[8]	2000	Crossover RCT	++	45 asthmatic children (5-14) on >400 mcg ICS and still symptomatic. Addition of salmeterol 50 and 100 mcg each bd were compared with salbutamol 200 mcg qds. Study period of 4 weeks.	FEV_1, PEFR am/pm Histamine challenge, PC20 Symptom scores Use of rescue medication	*compared salmeterol with addition of salbutamol am PEFR increased by 9.6 l/min and 13.8 l/min for salmeterol 50 and 100 mcg Salmeterol 50 – 1.54 Salmeterol 100 – 1.23 Median daytime score reduced from 1 to 0 for all treatments Days without rescue medication increased for all groups compared with baseline: 65% salbutamol, 61% salme. 50 and 72% salmet.100	95% ci 95% ci 2.1 to 17 95% ci 6 to 21-5 p<0.05 ci 0.65 to 3.7 ci 0.55 to 2.78 NS between treatment groups	No difference between the two doses (50/100) of salmeterol. No placebo, comparisons with baseline and salbutamol. Salmeterol signigicantly improved PEFR over 4 weeks.
Heuck[9]	2000	Randomised double-blind, placebo	+ primary objective	27 asthmatics, 6-13 y, whose asthma	Secondary variables 1) symptoms	Compared to BUD 200 mcg BD at baseline		Symptoms and lung function secondary

		controlled crossover trial	was study of bone turnover.	currently controlled on BUD 200 mct BD. Treatment formoterol 12mcg+ BUD100 v BUD200 mcg BD over 2*6 week periods	day/night (0-3 scores) 2) rescue med. Use 3) FEV1/FVC	1] Day p=0.55, 95%ci-0.11,0.2 Night p=0.64,95%ci-0.1, 0.15 2] p=0.56, 95%ci-0.11, 0.2 Night p=0.64, 95%ci-0.1, 0.15 2] p=0.56, 95%ci –0.48, 0.27 puffs/d 3] PEV1 higher at week 2 (p=0.04, 95%ci –0.01, 0.17, NS at week 6 (p=0.32, 95%ci –0.02, 0.06		variables. BUD 100mcg BD + Formoterol as good as BUD 200mcg BD- no loss of asthma control This intervention associated with better short term growth.
Russell[10]	1995	Randomised, placebo controlled, double blind	++	210 Symptomatic asthmatic children (4-16y) on ICS (> 400 mcg/d) treated with Salmeterol (50mcg Bd) or placebo for 12 weeks	1] max. proportion symptom free days (%)/nights (%) salmeterol 60%/81% placebo 26%/59% 2] median change in rescue med use –0.7 and –0.8 at 9-12 weeksfor salmeterol versus –0.3 for placebo 30 mean am PEFR (percentage points] was > 8 above baseline for weeks 4-12. Max. increase with placebo was 5. Mean pm PEFR greater for salmeterol than placebo by at least 1 percentage point	1] max. proportion symptom free days (%)/nights (%) salmeterol 60%/81% placebo 26%/59% 2] median change in rescue med use –0.7 and –0.8 at 9-12 weeksfor salmeterol versus –0.3 for placebo 30 mean am PEFR (percentage points] was >8 above baseline for weeks 4-12. Max. increase with placebo was 5. Mean pm PEFR greater for salmeterol than placebo by at least 1 percentage point	Comparison with placebo P>0.05 P>0.05 P>0.05 P>0.05 only for first 4 weeks	Improvement was better for salmeterol group at all times in 12 weeks compared with placebo

Langton Hewer[11]	1995	RCT double-blind Placebo controlled	+	24 children, 12 →17 yrs on "high doxe" ICS (not deferred) 50-1000mcg, medicine 400BD Received Salmeterol 100mcg BD or placebo for 8 weeks	1] Day/night symptoms PEFR am/pm 2] FEV1 (clinic)	Salmeterol v placebo 1] No stats given (wide range of values) this showed trend to improvement. 2] tend to improve Change from baseline significantly better for salmeterol • Change in am FEV1 +0.22 v's-0.2 (placebo) P< 0.05, 95%ci 0.65 to 0.12 • Change in pm FEV1 + 0.2 v's –0.16 (placebo) P< 0.05, 95%c1 0.67-0.07		
Tomac[12]	1996	Cohort study	+	24 asthmatic children (7-16) on ICS and/or DSC were treated with salmeterol 50 mcg BD for 4 weeks. Comparisons made with 2 week run-in	Rescue salbutamol Daily/nocturnal symptoms am/pm PEFR FEV1, FVC Airways resistance	Reduced on salmeterol compared with run-in period Reduced by salmeterol Am increased by 42 l/min, pm increased by 35 l/min No change in FEV1, MEF but FVC increased. sRaw decreased by 26%	P<0.02 P<0.05 P<0.001 NS for FVC P<0.05	Not an RCT, and includes concomitant medication – theophylines and DSC. Difficult to interpret.

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