

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Levalbuterol
11/2005

Recommendations:

Levalbuterol is non-formulary. Albuterol has been previously approved for automatic substitution at an equivalent dose for levalbuterol (two times levalbuterol dose at the same frequency).

- All patients receiving levalbuterol will be converted to an equivalent dose of albuterol after 48 hours of therapy, unless they are allergic to albuterol, receiving levalbuterol at home, or have acute atrial fibrillation. Objective parameters will be monitored by respiratory therapy (heart rate, tremors, nervousness, and blood gases if ordered) from start of levalbuterol to 48 hours after albuterol is started. If a clinically significant decline is not seen, albuterol will be continued.
- Data will be collected on all patients, during levalbuterol administration and after conversion to albuterol. This information will be presented to the committee for their review. (see accompanying monitoring tool).
- Currently Levalbuterol accounts for 19% of doses, but 87% of \$125,628 in total cost.

Findings:

- Bon Secours Richmond length of stay and mortality data, shows no advantage to levalbuterol over albuterol, see graphics below.
- FEV₁ increase is equivalent, approximately 30%.
- Duration of bronchodilation is equivalent, approximately 5-6 hours.
- Levalbuterol is R-isomer of racemic albuterol (1:1 ratio of R and S isomers)
- Half-life is the same with repeated doses (4 hours).
- Equivalent doses are a 2:1 ratio (1.25 mg of albuterol is equivalent to 0.63 mg of levalbuterol) for bronchodilation and side effects.
- Levalbuterol cost 22-44 times albuterol 2.5mg/3ml and albuterol solution respectively.
 - *All beta agonists current on the market are racemic mixtures except for levalbuterol.*
 - Side effects (heart rate increase, rise in serum potassium, and change in serum glucose) are similar for levalbuterol and albuterol at equivalent doses.
- Regular (scheduled) treatment with levalbuterol or racemic albuterol results in partial loss of broncho protection as compared with placebo.
- S-albuterol does not convert to R-albuterol in vivo.
- R-albuterol has been shown to convert to S-albuterol in one study in vivo.
- Doses of albuterol and levalbuterol used clinical are on the flat portion of the dose response curve.
- The S isomer is inert and does not inhibit the bronchodilator or broncho protective effects of R-albuterol. The S isomer does not induce tolerance to racemic albuterol, does not increase airway hyperresponsiveness, and does not cause systemic side effects.
- Changes in heart rate, length of ED care, and side effects are similar for the two products as demonstrated in the following studies
 - Ann Emerg Med 2005;46:29-36 Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. (prospective, double-blinded, randomized controlled trial)
 - J Emerg Med. 2005 Jul;29(1):29-35. Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: a prospective, double-blinded, randomized controlled trial.
 - Pediatr Emerg Care. 2005 Jul;21(7):415-9. Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. [Hardasmalani MD](#), [DeBari V](#), [Bithoney WG](#), [Gold N](#).
 - Am J Health Syst Pharm. 2003 Oct 1;60(19):1971-5. Changes in heart rate associated with nebulized racemic albuterol and levalbuterol in intensive care patients.
- An editorial by Ahrens R, Weinberger M Journal of Allergy and Clinical Immunology 2001;108:681-685 examines the weight of evidence form all of the published clinical trials that attempted to test the hypothesized benefits for using levalbuterol versus albuterol. The authors conclude:
 - Studies claiming a higher potency for levalbuterol did not demonstrate a dose response relationship for the doses of levalbuterol administered and were inadequately designed to show a difference when compared to albuterol.
 - Only one study, [Lotvall J. J Allergy Clin Immunol 2001;108:726-32](#), has been adequately designed and found no difference in potency when equivalent doses were administered.
 - Bronchoprotective effects against methacholine challenge of levalbuterol and albuterol are equivalent.
 - The weight of evidence supports neither the concept that S-albuterol works in opposition to bronchodilator and bronchoprotective effects of R-albuterol nor the concept that there is any difference in R-albuterol potency when it is administered as a single enantiomer rather than in a racemic formulation.
 - [Crockcroft DW. J Allergy Clin Immunol 1999;103:1049-53](#) demonstrate an equivalent of degree of tolerance after 6 days of levalbuterol and albuterol to methacholine challenge. The inactive isomer, S-albuterol, did not induce tolerance.

- Studies do not support the claim that S-albuterol increases airway hyperresponsiveness.
- All observed systemic effects of racemic albuterol are due to the R-enantiomer. The S-isomer is inert.
- The available data provide no evidence that levalbuterol is any safer or more effective than doses of racemic albuterol that contain equimolar doses of R-albuterol.

Cost Analysis:

Drug	Cost per Box	Cost per Dose
Levalbuterol (Xopenex®) 0.31 mg/3ml	\$53.87 per 24	\$2.24
Levalbuterol (Xopenex®) 0.63 mg/3ml	\$53.87 per 24	\$2.24
Levalbuterol (Xopenex®) 1.25 mg/3ml	\$53.87 per 24	\$2.24
Albuterol 2.5 mg/3ml UD	\$3.19 per 25	\$0.104
Albuterol 5 mg/ml 20 ml	\$2.68 for 40 doses	\$0.047

Potential Cost Impact of using levalbuterol in place of albuterol:

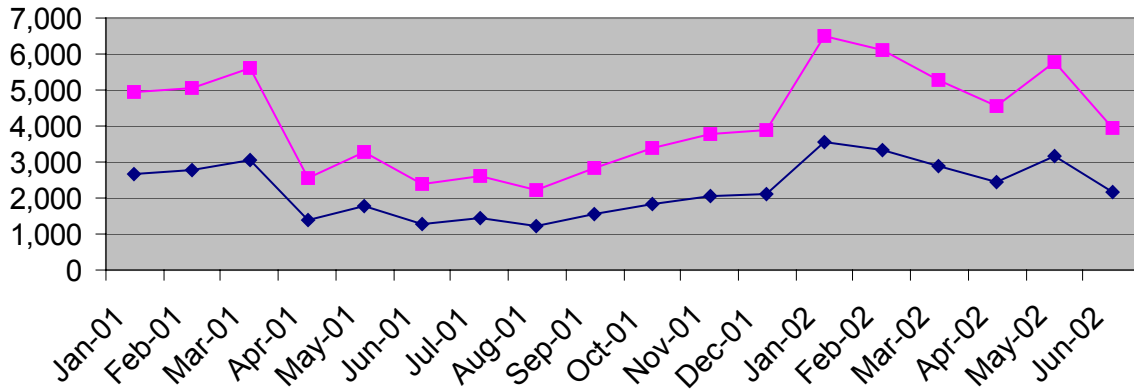
208,130 doses per year @ \$2.24/dose = \$466,211

Potential Cost Saving by converting levalbuterol to albuterol is \$104,648 per year.

2004-2005 Usage Data										
	Cost Per Unit	MRMC		RCH		SMH		BSR		Total Cost
		% of Doses	% of Cost	% of Doses	% of Cost	% of Doses	% of Cost	% of Doses	% of Cost	
Albuterol 2.5 mg/3ml	\$0.104	76.0	23.1	76.0	64.2	24.2	4.3	41.7	8.9	\$11,154.00
Albuterol 5 mg/ml-20ml	\$0.047	12.5	1.7	22.5	8.6	51.9	4.2	39.3	3.8	\$4,741.36
Xopenex 0.31mg/3ml	\$2.24	0.0	0.0	0.0	0.0	0.4	1.6	0.3	1.3	\$1,616.10
Xopenex 0.63mg/3ml	\$2.24	5.8	37.7	1.1	19.8	14.4	55.1	11.2	51.2	\$64,374.65
Xopenex 1.25mg/3ml	\$2.24	5.7	37.5	0.4	7.4	9.1	34.8	7.6	34.8	\$43,742.44

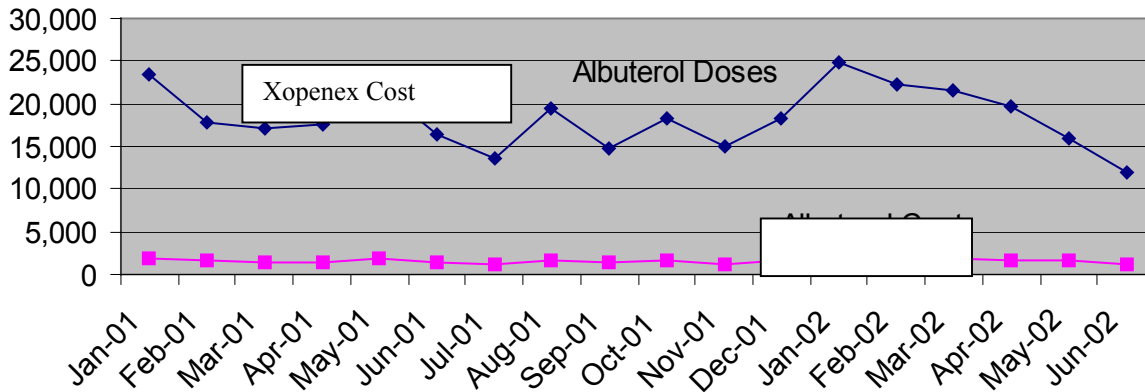
Cost Versus Doses Administered

◆ Total Xopenex Doses ■ Total Xopenex Cost \$



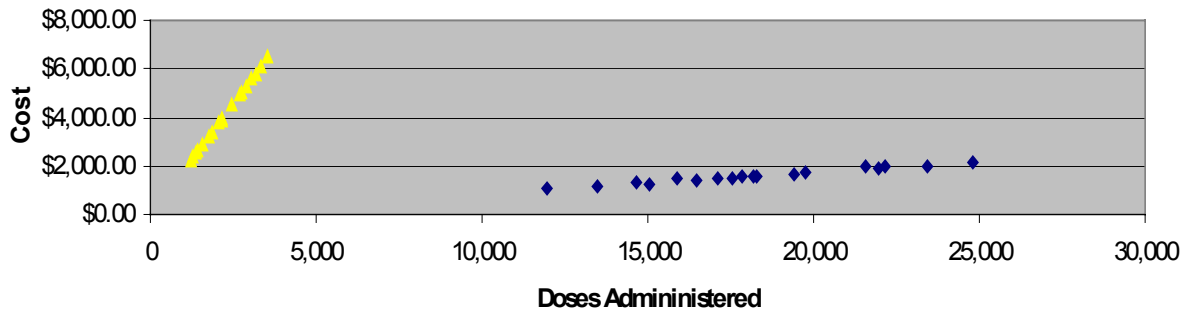
Cost Versus Doses Administered

◆ Total Albuterol Doses ■ Total Albuterol Cost

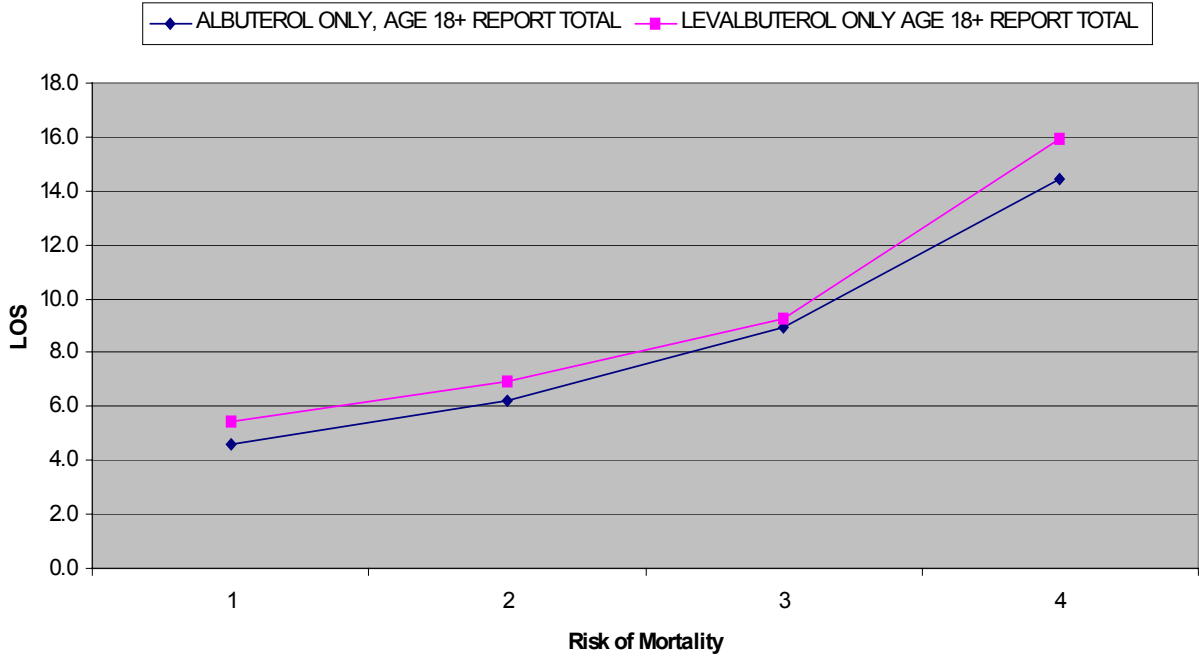


Cost of Xopenex Versus Albuterol

◆ Albuterol Cost \$ ▲ Xopenex Cost \$



Albuterol Versus Levalbuterol LOS



Albuterol Versus Levalbuterol Mortality



**Comparison of Albuterol Versus Levalbuterol
Bon Secours Richmond Data for FY01 and September - July 2002**

	Number of Cases	Length of Stay	% Mortality
Minor Risk of Mortality			
Albuterol	2575	4.6	0.5% (12/2575)
Levalbuterol	149	5.5	0.7% (1/149)
Moderate Risk of Mortality			
Albuterol	2410	6.2	2.7% (65/2410)
Levalbuterol	185	6.9	3.8% (7/185)
Major Risk of Mortality			
Albuterol	2470	9	7.4% (184/2470)
Levalbuterol	234	9.2	6.8% (16/234)
Extreme Risk of Mortality			
Albuterol	1460	14.5	24.2% (354/1460)
Levalbuterol	180	16	35.6% (64/180)

Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. (prospective, double-blinded, randomized controlled trial)

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STUDY OBJECTIVE: An efficacy treatment study is conducted comparing levalbuterol to racemic albuterol for acute pediatric asthma in the emergency department (ED). **METHODS:** This was a prospective, double-blind, randomized, controlled study involving 129 children (2 to 14 years), presenting to a pediatric ED with an acute moderate or severe asthma exacerbation (clinical asthma score greater than 8 or a forced expiratory volume in 1 second less than 70% of predicted). Exclusion criteria included: use of ipratropium or levalbuterol within 24 hours of presentation to the ED, use of oral or parenteral steroid within the past week, use of inhaled steroid greater than 400 mcg per day of beclomethasone or its equivalent in the past week, history of chronic underlying lung disease, history of heart disease. Children were treated using a standard ED asthma pathway, the first three nebulization treatments were given at 20 minute intervals, with subsequent treatments given at 30-60 minutes intervals at the discretion of the physician. Ipratropium therapy was delayed until after the third nebulized study treatment. Children weighing less than 25 kg received 2.5 mg of racemic albuterol or 1.25 mg or levalbuterol for each treatment. Children weighing 25 kg or greater received 5 mg of racemic albuterol or 2.5 mg of levalbuterol for each treatment. All children received 2 mg/kg of prednisone or equivalent corticosteroid by mouth with the second albuterol treatment. Primary outcomes were changes from baseline in clinical asthma score and the percentage of predicted forced expiratory volume in 1 second after the first, third, and fifth treatment. Secondary outcomes included number of treatments, length of ED care, rate of hospitalization, and changes in pulse rate, respiratory rate, and oxygen saturation. Occurrence of adverse events was recorded. **RESULTS:** Sixty-four children in the racemic albuterol and 65 children in the levalbuterol group completed the study. There were no differences between groups in primary outcomes, secondary outcomes, or adverse events. **CONCLUSION:** There was no difference in clinical improvement in children with acute moderate to severe asthma exacerbations treated with either racemic albuterol or levalbuterol.

Table 1. Baseline patient characteristics.

Patient Characteristics	Levalbuterol N=65	RS-Albuterol N=64
Median age, y (IQR)	6 (3, 8)	5.5 (3, 9)
Male, No. (%) [*]	52 (80)	33 (52)
Black, No. (%)	54 (83)	54 (84)
Median height, cm (IQR)	132 (113, 148)	122 (114, 140)
Median weight, kg (IQR)	22 (16, 36)	22 (16, 29)
Previous medication use, %		
β-Agonist	78	77
Inhaled steroids	28	16
Singulair	14	6
Severity of asthma (%)		
Moderate	63	69
Severe	37	31
Median asthma score (IQR)	10 (9, 12)	10 (9, 12)
Median FEV ₁ % predicted (IQR) [†]	25 (21, 34)	27 (25, 32)

IQR, Interquartile range (25th percentile, 75th percentile).
^{*}Significant difference between groups at $\alpha=0.05$ using χ^2 .
[†]Levalbuterol (N=24) and racemic albuterol (N=22).

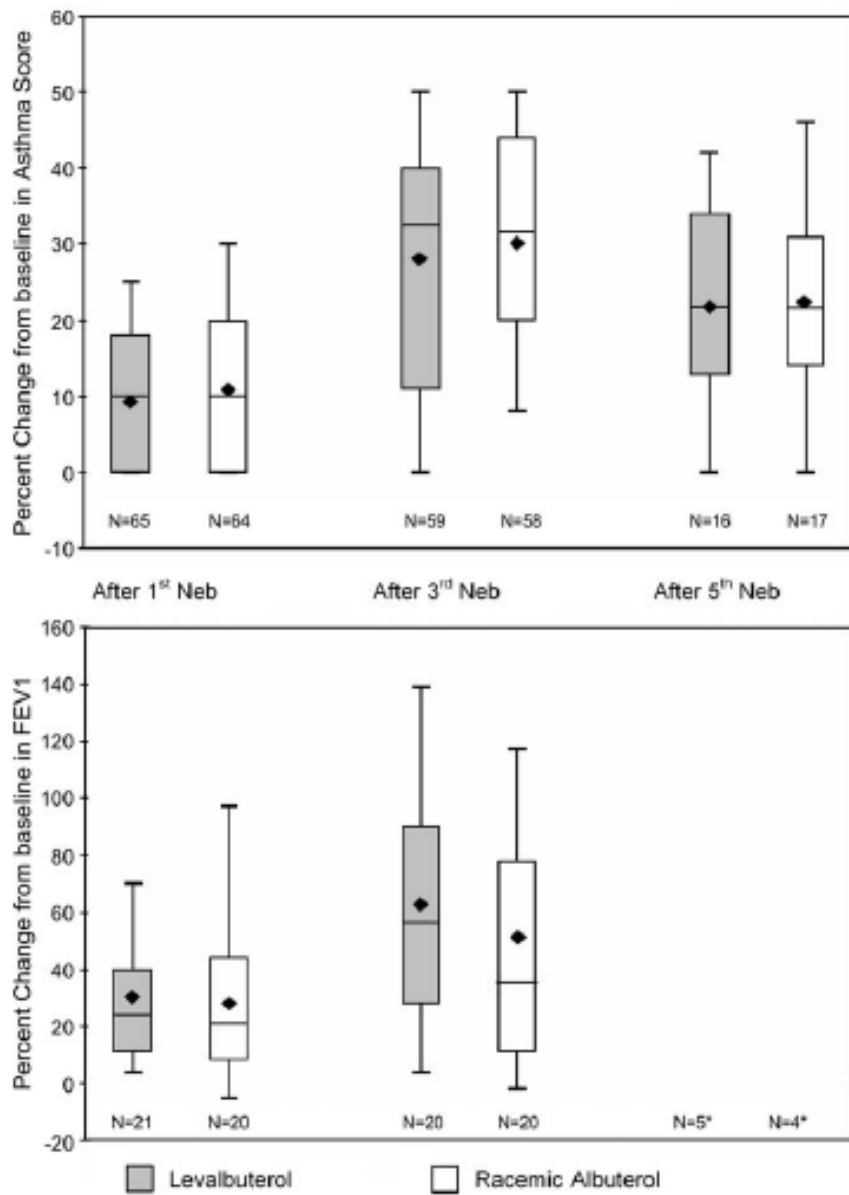


Figure 2. Primary outcomes by treatment group. Data are presented as box plots in which the diamond represents the mean and the 5 horizontal lines represent the 90th, 75th, 50th, 25th, and 10th percentiles. *Analyses not conducted because of low number of subjects.

Table 2. Secondary outcomes by treatment group.

	Levalbuterol N=65	RS-Albuterol N=64
Median number of nebulizations (IQR)	3 (3, 4)	3 (3, 5)
Median length of care, minutes (IQR)	121 (90, 160)	125 (95, 167)
Patients hospitalized, No. (%)	7 (11)	8 (13)
Median change in pulse rate (IQR)*		
After first nebulization	+9 (0, +14)	+8 (0, +16)
After third nebulization [†]	+22 (+15,+28)	+21 (+12, +29)
After fifth nebulization [‡]	+18 (+9, +31)	+18 (+9, +26)
Median change in respiratory rate (IQR)		
After first nebulization	-2 (-4, +2)	-2 (-4, 0)
After third nebulization [†]	-4 (-8, 0)	-4 (-8, 0)
After fifth nebulization [‡]	-5 (-12, -1)	-4 (-6, -2)
Median change in pulse oximetry, % (IQR)		
After first nebulization	+1 (0, +3)	+1 (0, +3)
After third nebulization [†]	+1 (-1, +3)	+1 (-1, +2)
After fifth nebulization [‡]	+1 (-1, +4)	-1 (-2, 0)

IQR, Interquartile range (25th percentile, 75th percentile).
*Changes in pulse rate, respiratory rate and pulse oximetry are from baseline.
[†]Levalbuterol (N=59) and racemic albuterol (N=58).
[‡]Levalbuterol (N=16) and racemic albuterol (N=17).

Table 3. Prevalence of adverse events.

	Levalbuterol, No. (%) (N=65)	RS-Albuterol, No. (%) (N=64)
Tremulousness	24 (37)	21 (33)
Nausea/vomiting	5 (8)	11 (17)
Headache	8 (12)	4 (6)
Lightheadedness	9 (14)	3 (5)
Drop in potassium <3.0 meq/L	3 (5)	3 (5)
Other*	1 (2)	1 (2)

*One child receiving racemic albuterol had tachycardia >200 beats/min. One child receiving levalbuterol had an elevated temperature (38°) before discharge.

Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: a prospective, double-blinded, randomized controlled trial.

[Ralston ME](#), [Euwema MS](#), [Knecht KR](#), [Ziolkowski TJ](#), [Coakley TA](#), [Cline SM](#).

Department of Emergency Medicine, Naval Medical Center, Portsmouth, Virginia, USA.

Our study compared levalbuterol (LEV) to the combination of racemic albuterol (RAC) and ipratropium bromide (IB) in 140 patients aged 6-18 years presenting to a tertiary hospital Emergency Department with acute asthma and a peak expired flow rate (PEF) < 80% predicted. Patients were randomized to: LEV (≤ 6 nebs LEV 1.25 mg); or RAC/IB (≤ 3 nebs RAC 5.0 mg + IB 0.25 mg followed as needed by ≤ 3 nebs RAC 5.0 mg). No difference was noted in the study population (mean age 11.6 years and initial mean predicted PEF 49.5%) between LEV (n=72) and RAC/IB (n=68) for study outcomes (number of nebulized treatments, PEF measurements, symptomatic complications, or unplanned return visits for asthma management) except for measures of heart rate (HR). Median % HR increase for RAC/IB (26%) exceeded LEV (9%) (p<0.001). In a sample of children with acute asthma and initial mean PEF<50% predicted, LEV was associated with less tachycardia but had no other advantage over RAC combined with IB. **Note: Study dose of albuterol is twice the equivalent dose of levalbuterol.**

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	LEV 1.25 mg (n = 72)	RAC 5.0 mg + IB .25 mg (n = 68)	p Value
Age, years mean (SE)	11.7 (0.4)	11.5 (0.4)	0.810
Gender no. (%)			0.323
Male	42 (58)	34 (50)	
Female	30 (42)	34 (50)	
Race no. (%)			0.464
African-American	34 (48)	39 (59)	
Caucasian	30 (42)	21 (32)	
Hispanic	4 (6)	2 (3)	
Other	3 (4)	4 (6)	
Home medications no. (%)			0.849
Inhaled steroids	25 (35)	27 (40)	
Oral steroids	2 (3)	2 (3)	
Montelukast	12 (17)	9 (13)	
Salmeterol	6 (8)	4 (6)	
Weight, kg mean (SE)	47 (2.1)	47 (2.5)	0.959
Height, cm mean (SE)	148 (1.9)	147 (2.2)	0.795
Initial vital signs			
SaO ₂ (room air) % mean (SE)	97 (0.3)	97 (0.3)	0.878
Heart rate beats/min mean (SE)	103 (2.4)	100 (2.5)	0.449
Resp. rate beats/min mean (SE)	24 (0.9)	23 (0.8)	0.307
Initial PEF			
L/min mean (SE)	176 (8.5)	166 (8.5)	0.374
% Predicted mean (SE)	51 (1.9)	48 (1.8)	0.350
< 50% Predicted # (%)	33 (46)	35 (51)	0.505
50-80% Predicted # (%)	39 (54)	33 (49)	

Table 2. Efficacy Outcomes

Outcome	LEV 1.25 mg (n = 72)	RAC 5.0 mg + IB .25 mg (n = 68)	p Value
ED LOS min median (Q ₁ , Q ₃)	80 (60, 122)	94 (70, 133)	0.130
Increase PEF _{INITIAL} to FINAL % median (Q ₁ , Q ₃)	45 (18, 87)	61 (28, 99)	0.365
Increase PEF _{INITIAL} to MAX % median (Q ₁ , Q ₃)	49 (21, 89)	61 (30, 99)	0.424
Nebs # mean (SE)	2.8 (0.2)	2.7 (0.1)	0.718
Time between nebs min mean (SE)	26 (1.0)	26 (1.6)	0.257
Received nebs 1-3 # (%)	58 (81)	57 (84)	0.782
Received nebs 4-6 # (%)	14 (19)	11 (16)	0.549
Oral steroids in ED # (%)	50 (70)	59 (87)	0.014
i.v. Steroids in ED # (%)	1 (1)	0 (0)	1.00
No adjunctive meds in ED # (%)	21 (29)	9 (13)	0.022
72 h Return for asthma # (%)	1 (1)	0 (0)	1.00

Table 3. Safety Outcomes

Outcome	LEV 1.25 mg (n = 72)	RAC 5.0 mg + 1B .25 mg (n = 68)	p Value
HR _{FINAL} beats/min mean (SE)	114 (2.7)	126 (3.0)	0.003
HR _{MAX} beats/min mean (SE)	119 (3.1)	130 (3.4)	0.019
Increase HR _{INITIAL} to FINAL			
Beats/min mean (SE)	10 (3.0)	26 (2.8)	< 0.001
% Median (Q ₁ , Q ₃)	8 (-1, 23)	20 (13, 43)	< 0.001
Increase HR _{INITIAL} to MAX			
Beats/min mean (SE)	16 (3.0)	29 (3.1)	0.002
% Median (Q ₁ , Q ₃)	9 (2, 27)	26 (14, 48)	< 0.001
HR _{MAX} above normal range for age # (%)	35 (51)	47 (73)	0.009
New symptoms no. (%)			
Tremor	17 (24)	20 (29)	0.437
Nervousness	8 (11)	13 (19)	0.165
Nausea or vomiting	2 (3)	6 (9)	0.157
Palpitations	5 (7)	9 (13)	0.215
Headache	6 (8)	9 (13)	0.349
Any symptoms	29 (40)	33 (49)	0.326

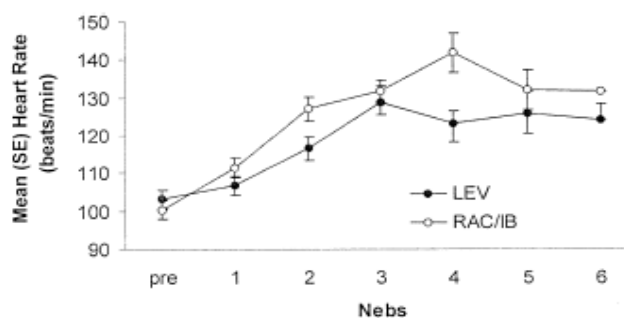


Figure 2. Effect of LEV and RAC/IB on heart rate.

Pediatr Emerg Care. 2005 Jul;21(7):415-9.

Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children.

[Hardasmalani MD](#), [DeBari V](#), [Bithoney WG](#), [Gold N](#).

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OBJECTIVE: To compare levalbuterol and racemic albuterol for the treatment of acute exacerbation of asthma in pediatric population. **DESIGN:** Prospective, double-blind, randomized research trial in a pediatric emergency department of an urban tertiary care hospital. **PARTICIPANTS:** Children 5 to 21 years with a history of asthma presenting to the emergency department in acute exacerbation. **INTERVENTIONS:** As per a computer-generated randomization sequence, patients received (either 1.25 mg of levalbuterol or albuterol 2.5 mg via nebulization) along with ipratropium hydrochloride. Patients received 3 back-to-back treatments as needed every 20 minutes, maximum of 3; 2 mg/kg of oral prednisone was administered to the patients after the second treatment. Baseline respiratory parameters such as oxygen saturations, respiratory rates, and peak flow rates were measured and repeated after every treatment. The decision for further treatments and or hospitalization was made by the treating emergency department physician as per his/her clinical judgement of the respiratory parameters at the end of 3 treatments. **RESULTS:** Seventy patients completed the study. Most of the patients were in moderate severity of asthma exacerbation. All patients in both groups showed improvement in oxygen saturations, respiratory rates, and peak flow rates. However, no statistically significant difference was observed in the 2 groups regarding the respiratory parameters ($P > 0.05$) or hospital admission rate or need for extra treatments in ED. **CONCLUSION:** Levalbuterol is not more efficacious than racemic albuterol in improving respiratory parameters in children presenting with acute exacerbation of asthma.

TABLE 1. Characteristics of Patients in the Test Groups

	R-S Albuterol (n = 30)	LEV (n = 33)	95% CI of the Significance Difference*	(2-tailed)*
Age (y)				
Mean [†]	13.03 ± 4.55	11.33 ± 4.37	-547 to 3.947	.135
Sex (1 M, 2 F)				
Mean [†]	1.53 ± 0.51	1.38 ± 0.49	-0.095 to 0.389	.230
Height (in)				
Mean [†]	59.68 ± 6.27	58.92 ± 7.77	2.8076 to 4.3187	.673

Independent samples *t* test for equality of means (95% confidence interval [CI] of the difference).
*Equal variances assumed.
[†]Mean ± 1 SD.

TABLE 2. Prestudy Physiological Parameters of Patients

	R-S Albuterol (n = 34)	LEV (n = 36)	95% CI of the Significance Difference*	(2-tailed)*
Saturation/first				
Mean [†]	96.82 ± 2.24	96.53 ± 2.26	-0.78 to 1.37	0.5840
Respiratory rate/first				
Mean [†]	25.50 ± 6.54	26.40 ± 7.19	-4.21 to 2.41	0.589
Peak flow rate/first				
Mean [†]	170.59	166.94	-38.66 to 45.95	0.8640

Independent samples *t* test for equality of means (95% CI of the difference).
*Equal variances assumed.
[†]Mean ± 1 SD.

TABLE 3. Poststudy Physiological Parameters of Patients

	R-S Albuterol (n = 30)	LEV (n = 33)	95% CI of the Significance Difference*	(2-tailed)*
Saturation difference				
Mean [†]	1.41 ± 1.76	1.42 ± 1.54	-0.79198 to 0.78218	.990
Respiratory rate difference				
Mean [†]	-3.50 ± 3.84	-3.77 ± 6.02	-2.18030 to 2.70971	.830
Peak flow rate difference				
Mean [†]	97.35 ± 77.55	95.14 ± 63.06	-31.412 to 35.840	.896
Peak flow rate percent change				
Mean [†]	70.37 ± 53.89	66.03 ± 41.67	-18.56267 to 27.24094	.707

Independent samples *t* test for equality of means (95% CI of the difference).
*Equal variances assumed.
[†]Mean ± 1 SD.

Allergy Asthma Proc. 2004 Nov-Dec;25(6):429-36.

Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma. Sepracor Study

[Pleskow WW](#), [Nelson HS](#), [Schaefer K](#), [Claus R](#), [Roach JM](#).

Radiant Research, Encinitas, California, USA.

The object of this study is a *post hoc* pairwise comparison of levalbuterol versus racemic albuterol for asthma in a multicenter, double-blind, randomized, placebo-controlled clinical trial. The participants are patients $> \text{ or } = 12$ years of age ($n = 362$) with FEV1 45-70% of predicted. The patients received nebulized levalbuterol (0.63 or 1.25 mg), racemic albuterol (1.25 or 2.5 mg), or placebo t.i.d. for 4 weeks. The primary endpoints, published in Nelson HS, Bensch G, Pleskow WW, et al. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 102:943-952, **1998**, included comparisons of active treatments with placebo and of the combined levalbuterol with the combined racemic albuterol groups for pulmonary function and rescue medication use. After the first dose, levalbuterol 1.25 mg produced a significantly greater increase in the mean peak change in FEV1 compared with both doses of racemic albuterol ($p < 0.03$) in all patients and in those with more severe asthma. Levalbuterol 1.25 mg also produced a significantly greater ($p < 0.05$) mean area under the curve (AUC) of the FEV1 versus time plot (AUC FEV1) compared with all other treatments after the first dose in all patients and in the subset with more severe disease, illustrating better overall improvement in FEV1. Active treatment groups demonstrated significant improvements compared with the placebo group ($p < 0.05$), except for AUC FEV1 in the racemic albuterol 1.25-mg group at week 4. Levalbuterol in the absence of the (S)-isomer provided greater bronchodilation than the same quantity of (R)-albuterol delivered as the racemate. These data suggest that (S)-albuterol may compromise the efficacy of (R)-albuterol.

Respir Med. 2004 Oct;98(10):990-9.

Single-isomer R-salbutamol is not superior to racemate regarding protection for bronchial hyperresponsiveness.

[Sjosward KN](#), [Hmani M](#), [Davidsson A](#), [Soderkvist P](#), [Schmekel B](#).

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Bronchial hyper-reactivity (BHR) has been suggested to follow cessation of regular medication with racemic salbutamol. This study aimed at investigating the effects from medication with R,S- and R-salbutamol on bronchial response to provocation with isocapnic hyperventilation of cold air (IHCA). Twenty-six patients with mild to moderate asthma were enrolled in a double-blind, randomised, cross-over study. Bronchial response to provocation was measured before and after 1 week's medication. Doses of 0.63 mg R-salbutamol or 1.25 mg R/S-salbutamol were inhaled three times daily during medication-weeks and a wash-out week intervened. Tests were performed 6 h after the last dose of test drug. Impulse oscillometry and forced expiratory volume during one second were methods used to identify bronchial response to provocation. Two patients withdrew from the investigation due to side-effects, one from R- the other from R,S-salbutamol. Comparable resting bronchial conditions were indicated by differences in baseline lung function values of $< 2\%$ between study days. No statistically significant medication-dependent differences in BHR could be demonstrated between treatment groups. However, 15 patients exhibited higher ($P = 0.03$) post-treatment BHR after pure R-salbutamol than after R,S-salbutamol. Furthermore, plasma concentrations of R-salbutamol tended to be lower ($P = 0.08$) after medication with R- than after R,S-salbutamol despite equal doses of R-salbutamol given during the two separate treatment periods. *We also found that considerable amounts of S-salbutamol were retrieved in plasma after medication with pure R-salbutamol.* We conclude that we were unable to demonstrate favourable effects of R-salbutamol over R,S-salbutamol regarding response to provocation with IHCA after regular medication of 1 week's duration.

Changes in heart rate associated with nebulized racemic albuterol and levalbuterol in intensive care patients.

[Lam S](#), [Chen J](#).

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The effects of equipotent doses of racemic albuterol and levalbuterol on heart rate (HR) in intensive care patients with and without baseline tachycardia were studied. Patients were included if they were hemodynamically stable and required bronchodilator therapy every four hours; patients were excluded if they were maintained on a beta-blocker. Four hours after the most recent bronchodilator treatment, each patient was randomized to receive at least two consecutive doses of albuterol 2.5 mg or levalbuterol 1.25 mg four hours apart via nebulization. HR was recorded at the end of the second dose and 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes after treatment. Twenty intensive care patients, including 10 with baseline tachycardia and 10 without baseline tachycardia, were enrolled. In patients with baseline tachycardia, the mean largest HR increase was 1.4 beats/min (1.3%) with albuterol and 2.0 beats/min (2.1%) with levalbuterol (both increases were not significant). In patients without baseline tachycardia, the mean largest HR increase was 4.4 beats/min (6.7%) with albuterol ($p = 0.04$) and 3.6 beats/min (5.0%) with levalbuterol ($p = 0.03$). Short-term use of nebulized albuterol and levalbuterol was associated with similar changes in HR in intensive care patients with or without baseline tachycardia.

Table 1.
Baseline Characteristics of Study Patients

Characteristic ^a	Value	
	Patients with Tachycardia (n = 10)	Patients without Tachycardia (n = 10)
Mean ± S.D. age (yr)	69.3 ± 14	55.6 ± 12
No. (%) men	6 (60)	3 (30)
Mean ± S.D. baseline HR (beats/min)		
Racemic albuterol	104 ± 11	71 ± 10
Levalbuterol	100 ± 10	78 ± 9
Reason for ICU admission, no. (%)		
Cardiovascular	5 (50)	1 (10)
Pulmonary	1 (10)	4 (40)
Other	4 (40)	5 (50)
Indication for bronchodilator, no. (%)		
COPD	2 (20)	1 (10)
Asthma	0	2 (20)
Other	8 (80)	7 (70)
Mean ± S.D. no. concomitant medications	8 ± 3	8 ± 2

^aHR = heart rate, ICU = intensive care unit, COPD = chronic obstructive pulmonary disease.

Table 2.

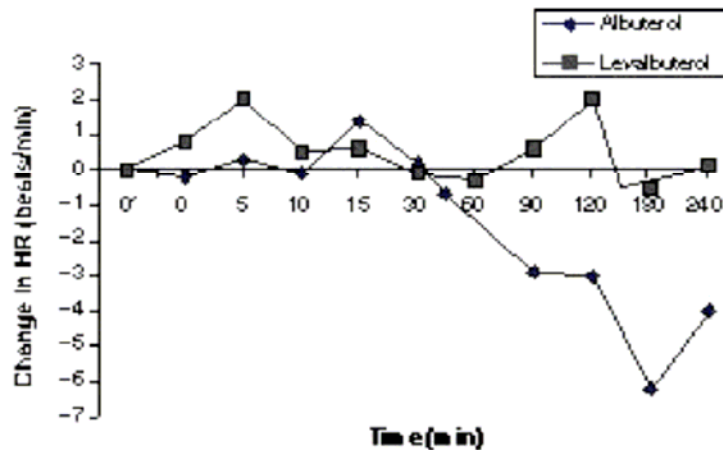
Effects on Heart Rate (HR) of Albuterol and Levalbuterol

Variable	Value	
	Albuterol	Levalbuterol
<i>Patients with Baseline HR > 90 Beats/Min</i>		
Mean \pm S.D. baseline HR (beats/min)	104 \pm 11	100 \pm 10
Mean \pm S.D. highest HR (beats/min)	105 \pm 12	102 \pm 10
Mean \pm S.D. largest HR increase (beats/min)	1.4 \pm 2.7	2.0 \pm 4.7
Time of highest mean HR (min)	15	5
Mean \pm S.D. largest HR decrease (beats/min)	6.2 \pm 8.9	0.5 \pm 10.7
Time of lowest mean HR (min)	180	180
<i>Patients with Baseline HR \leq 90 Beats/Min</i>		
Mean \pm S.D. baseline HR (beats/min)	71 \pm 10	78 \pm 9
Mean \pm S.D. highest HR (beats/min)	75 \pm 11 ^a	82 \pm 9 ^a
Mean \pm S.D. largest HR increase (beats/min)	4.4 \pm 7.2	3.6 \pm 5.3
Time of highest mean HR (min)	120	30
Mean \pm S.D. largest HR decrease (beats/min)	.. ^b	5.1 \pm 8.2
Time of lowest mean HR (min)	.. ^b	240

^aSignificantly different from the baseline value ($p < 0.05$, Student's *t* test).

^bMean HR did not drop below the mean baseline value.

Figure 1. Heart rate (HR) changes in patients with baseline tachycardia who received nebulized albuterol or levalbuterol. Time 0* = initiation of study drug administration, time 0 = end of study drug administration.



J Emerg Med. 2003 Jul;25(1):13-6.

Levalbuterol is as effective as racemic albuterol in lowering serum potassium.

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Albuterol is an effective treatment for hyperkalemia through beta-adrenergic induction of potassium (K⁺) uptake. Levalbuterol, the R-enantiomer of racemic albuterol, is used for the treatment of asthma and 0.63 mg of levalbuterol has the same therapeutic efficacy as 2.5 mg of albuterol but with a decreased adverse effects profile. We hypothesized that levalbuterol can reduce serum K⁺ levels similarly to albuterol when used in equipotent doses. In a randomized, double blind, placebo-controlled prospective study, we compared the K⁺-lowering effects of nebulized saline and equipotent bronchodilatory doses of albuterol (10 mg) and levalbuterol (2.5 mg) in healthy adult volunteers. Nine subjects entered each of the three study groups. Serum K⁺ was measured at baseline, at 30 min (immediately after treatment), at 60 min, and at 90 min. All adverse effects were recorded. The three groups had similar baseline K⁺ values. Immediately after nebulization, only levalbuterol showed a significant decrease in potassium level ($p = 0.024$). At 30 and 60 min after treatment, both albuterol and levalbuterol groups had significantly lower K⁺ values compared to placebo. No significant

difference occurred between the albuterol and levalbuterol groups. Levalbuterol caused fewer reported adverse effects compared to albuterol. Note: the dose of albuterol was twice the equivalent dose of levalbuterol.

Am J Emerg Med. 2004 Jan;22(1):29-36.

Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study.

Nowak RM, Emerman CL, Schaefer K, Disantostefano RL, Vaickus L, Roach JM.

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This was a prospective, *open-label, nonrandomized non-cross over pilot study* to evaluate efficacy and tolerability of levalbuterol (LEV) in acute adult asthma with 12-14 patients per treatment group. Asthmatics (forced expiratory volume in 1 second [FEV₁], 20-55% predicted) were sequentially enrolled into cohorts of 12 to 14 and received 0.63, 1.25, 2.5, 3.75, or 5.0 mg LEV or 2.5 or 5.0 mg racemic albuterol (RAC) every 20 minutes x 3. After the first dose, FEV₁ changes were 56% (0.6 L) for 1.25 mg LEV and 6% (0.07 L) and 14% (0.21 L) for 2.5 and 5 mg RAC respectively. After three doses, FEV₁ changes were 74% (0.9 L), 39% (0.5 L), and 37% (0.6 L) for 1.25 mg, LEV 2.5 mg, RAC and 0.63 mg LEV respectively. LEV doses greater than 1.25 mg did not further improve bronchodilation. Baseline plasma (S)-albuterol levels were negatively correlated with baseline FEV₁ (R = - 0.3, P = .004) and percent change in FEV₁ (R = -0.3, P = .006). LEV at a dose of 1.25 mg produced effective bronchodilation that was greater than both RAC doses. The negative correlation between (S)-albuterol levels and FEV₁ could suggest a deleterious effect of (S)-albuterol. Larger comparative studies are warranted. *Note: No adjustments were made for multiple comparisons, which violates statistical rules. No dose response relationship was demonstrated. This was not a cross over study; differences in outcomes could be attributed to patient differences and lack of randomization.*

Chest. 2003 Sep;124(3):844-9.

An evaluation of nebulized levalbuterol in stable COPD.

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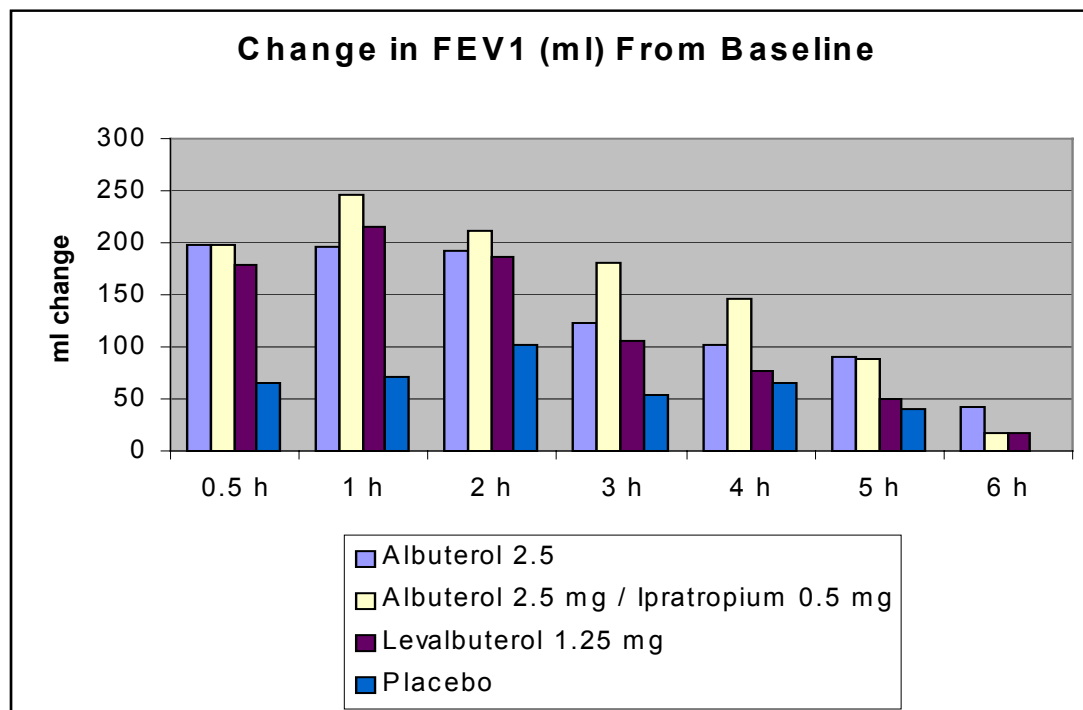
BACKGROUND: Levalbuterol, the R-isomer of albuterol, has advantages over racemic albuterol in asthma; however, the effectiveness of this beta-agonist in COPD has received little attention. **OBJECTIVES:** To evaluate the effectiveness of a single dose of nebulized levalbuterol in COPD. **DESIGN:** A randomized, double-blind, cross over, placebo-controlled trial comparing nebulized levalbuterol to racemic albuterol, combined racemic albuterol and ipratropium, and placebo. **PATIENTS:** Thirty patients with stable COPD (FEV₁ between 45% and 70% of predicted) were studied. **METHODS:** After withholding usual bronchodilator medications for appropriate washout periods, patients were randomized on separate visits to receive single doses of each the following nebulized bronchodilator medications: (1) levalbuterol, 1.25 mg; (2) racemic albuterol, 2.5 mg; (3) combined racemic albuterol, 2.5 mg, and ipratropium, 0.5 mg; or (4) placebo. FEV₁, FVC, pulse rate, and oxygen saturation were measured at baseline, 0.5 h following nebulization, and hourly for 6 h. Hand tremor, using a 7-point scale, was measured at baseline, 0.5 h, 1 h, and 2 h. Treatment-placebo differences were analyzed using repeated-measures analysis of variance and least-squares means. **RESULTS:** The mean age (+/- SD) of patients was 69 +/- 15 years. Mean FEV₁ was 1.15 +/- 0.49 L. By 0.5 h following study drug administration, all three nebulized bronchodilator treatments led to similar, significant improvements in FEV₁ compared to placebo. These effects persisted at 1 h and 2 h for all three treatments; however, by 3 h, only the combined albuterol/ipratropium group had a mean change in FEV₁ significantly greater than placebo. There were no significant differences between bronchodilator groups at any time period. A mild increase in pulse rate was observed in all treatment groups. There were no significant treatment-placebo differences in oxygen saturation or hand

tremor. CONCLUSION: For single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional nebulized bronchodilators.

Change in FEV1 (ml) From Baseline Following Study Drug							
	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h
Albuterol 2.5	199**	197*	193	124	102	91	43
Albuterol 2.5 mg / Ipratropium 0.5 mg	198**	247**	211*	180*	147	89	17
Levalbuterol 1.25 mg	178*	216**	186	105	77	50	17
Placebo	66	71	102	54	66	40	0

*p < 0.005 versus placebo

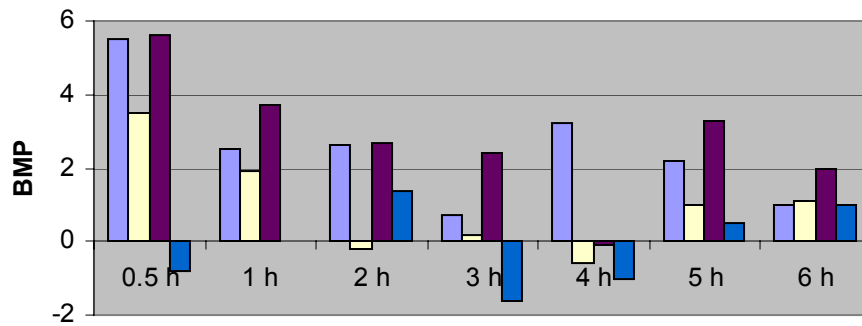
**p < 0.01 versus placebo



Change in Pulse Rate From Baseline Following Study Drug Administration							
	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h
Albuterol 2.5	5.5*	2.5	2.6	0.7	3.2	2.2	1
Albuterol 2.5 mg / Ipratropium 0.5 mg	3.5	1.9	-0.2	0.2	-0.6	1	1.1
Levalbuterol 1.25 mg	5.6*	3.7	2.7	2.4	-0.1	3.3	2
Placebo	-0.8	0	1.4	-1.6	-1	0.5	1

*p < 0.01 versus placebo

Change in Pulse From Baseline Following Study Drug Administration



- Albuterol 2.5
- Albuterol 2.5 mg / Ipratropium 0.5 mg
- Levalbuterol 1.25 mg
- Placebo

Comparison of racemic albuterol and levalbuterol for treatment of acute asthma.

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OBJECTIVE: To determine whether levalbuterol resulted in fewer hospital admissions than racemic albuterol when used for treatment of acute asthma. Study design A randomized, double-blind, controlled trial was conducted in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital. Children age 1 to 18 years (n=482) provided a total of 547 enrollments. Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum six doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome. **RESULTS:** Hospitalization rate was significantly lower in the levalbuterol group (36%) than in the racemic albuterol group (45 %, P=0.02). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% confidence interval, 1.01-1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; P=.63). No significant adverse events occurred in either group. **CONCLUSIONS:** Substituting levalbuterol for racemic albuterol in the ED management of acute asthma significantly reduced the number of hospitalizations. Note: An accompanying editorial notes objective criteria for hospital admission were not used and the similarity of objective ED measures in the treatment groups. Admission of asthma patients to the hospital is based on social and environmental criteria, availability of beds and past asthma history, not solely on the current medical issues.

Outcome	Albuterol 2.5 mg N=269	Levalbuterol 1.25 mg N=278	P Value
ED			
LOS mean (hours)	2.2 +/- 0.8	2.3 +/-0.9	NS
Aerosols, mean	4.1 +/-1.9	3.7 +/- 1.9	NS
Admission oxygen saturation, %	95.9 +/- 2.7	95.6 +/-2.8	NS
Discharge respiratory rate	35.6 +/- 12.6	37 +/- 10.4	NS
Intensified %	11.5	9	NS
Hospital Admission	45%	36%	P=0.02
Inpatient			
LOS mean (hours)	50.3 +/- 38.8	44.9 +/- 13.5	NS
Aerosols, mean	11.9 +/- 4.7	11.5 +/- 3.7	NS
Admission oxygen saturation	95.5 +/- 2.5	94.2 +/-6	NS
Patients requiring oxygen in any phase %	12.4	17.9	NS
Intensified %	16.5	10.1	NS
Heart Rate	130.1+/-23.3	129.7 +/- 25.5	NS

Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma.

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STUDY OBJECTIVES: To compare clinical efficacy, patient outcomes, and medical costs in hospitalized patients treated with levalbuterol to those treated with racemic albuterol. **DESIGN:** *Retrospective chart review in consecutive years.* **SETTING:** A 180-bed community hospital. **PATIENTS:** Patients admitted to Halifax Regional Hospital with a diagnosis code for COPD or asthma from July 1 to December 31, 1998 (albuterol), and from July 1 to December 31, 1999 (levalbuterol), were eligible. In 1998, 125 patients were treated with nebulized racemic albuterol (2.5 mg q4h). In 1999, 109 patients were treated with levalbuterol (1.25 mg q8h). **Measurements and results:** Clinical efficacy was evaluated by the number of nebulizer treatments, improvement in symptoms and objective clinical findings, the length of hospital stay, and hospital discharge disposition. Medication and total hospital costs were calculated based on Red Book listings and Medicare reimbursement rates. Levalbuterol-treated patients required significantly fewer treatments with beta-agonists (mean [+/- SD] number of treatments, 19.0 +/- 12.7 vs 30.8 +/- 24.0; $p < 0.001$) and ipratropium bromide (mean number of treatments, 9.4 +/- 11.5 vs 23.2 +/- 25.1; $p < 0.001$) than did racemic albuterol-treated patients. The mean length of hospital stay in the levalbuterol group was almost 1 day less than that in the racemic albuterol group (4.7 +/- 2.9 vs 5.6 +/- 4.2 days, respectively; $p < 0.058$). Significantly more patients were readmitted to the hospital within 30 days in the racemic albuterol group compared with the levalbuterol group (16.4% vs 5.7%, respectively; $p = 0.01$). The mean total cost of nebulizer therapy was significantly greater for patients receiving racemic albuterol than for those receiving for levalbuterol (\$112 +/- 101 vs \$61 +/- 43, respectively; $p < 0.001$). The mean total hospital costs per patient were less for levalbuterol compared with racemic albuterol (\$2756 +/- 2079 vs \$3225 +/- 2714, respectively; $p = 0.11$). Regression analysis controlling for diagnosis, baseline FEV₁(1), and ipratropium use indicated that levalbuterol was associated with a length-of-stay savings of 0.91 days ($p = 0.015$), a total cost savings of \$556 ($p = 0.013$), and a decrease in the likelihood of hospital readmission of 67% ($p = 0.056$). **CONCLUSION:** Compared with patients treated with racemic albuterol, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appeared to have a more prolonged therapeutic benefit. These findings support using levalbuterol as first-line therapy for hospitalized adults with COPD or asthma.

	Asthma		COPD	
	Albuterol N=35	Levlbuterol N= 19	Albuterol N=90	Levalbuterol N=87
Admission FEV1 L*	1.28	1.42	0.95	0.87
% Predicted*	44.6	48.6	36.2	32.9
Discharge FEV1*	1.75	1.85	1.03	0.99
% Predicted*	57	63.4	36.7	37.1
Admission FVC L*	1.89	2.14	1.57	1.48
Discharge FVC L*	2.38	2.49	1.75	1.68
Length of stay days	4.5	3.3	6.1	5.1
% Readmitted within 30 days	0*	5.3*	23**	5.8**

* No significant difference among treatment groups

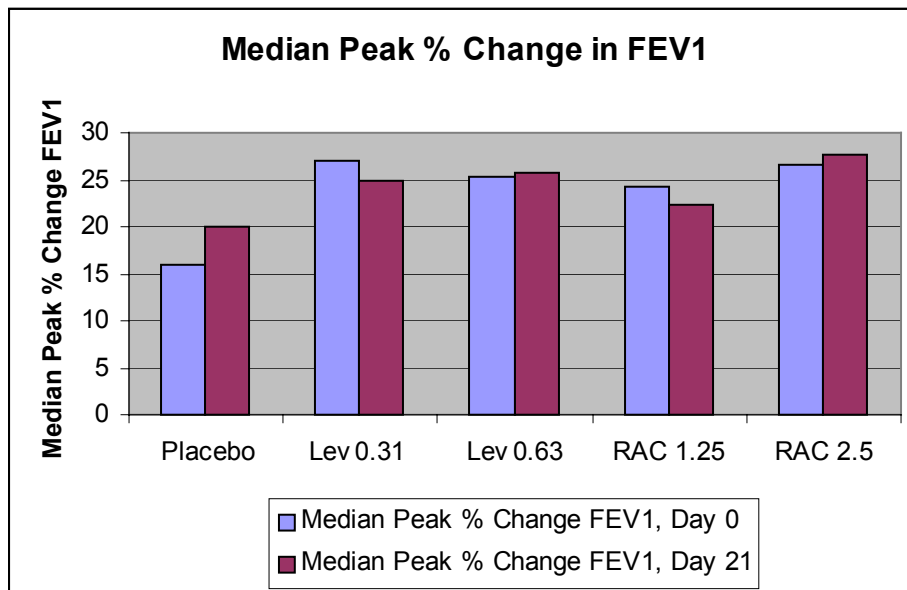
** $p = 0.0012$

Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol.

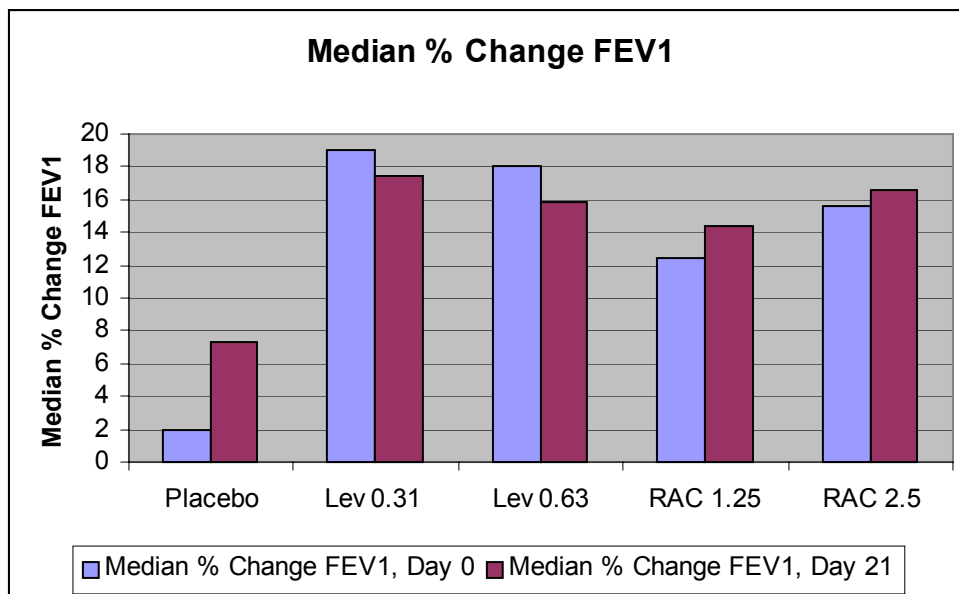
Milgrom H, Skoner DP, Bensch G, Kim KT, Claus R, Baumgartner RA; Levalbuterol Pediatric Study Group.

National Jewish Medical and Research Center, Denver, Colorado, USA.

BACKGROUND: Racemic albuterol (RAC) is an equal mixture of (R)-albuterol and (S)-albuterol. Only the (R)-isomer, levalbuterol (LEV), is therapeutically active. Lower doses of LEV, devoid of (S)-albuterol, have demonstrated efficacy comparable to that of higher doses of the (R)-isomer administered as a component of RAC. **OBJECTIVE:** The purpose of this study was to determine whether LEV results in improved safety and efficacy in children. **METHODS:** Asthmatic children aged 4 to 11 years ($n = 338$; FEV₁, 40% to 85% of predicted) participated in this multicenter, randomized, double-blinded study and received 21 days of 3-times-a-day treatment with nebulized LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo. The primary endpoint was FEV₁ (peak percent change). Adverse events, clinical laboratory test results, vital signs, and electrocardiograms were evaluated for safety. **RESULTS:** All active treatments significantly improved the primary endpoint in comparison with placebo ($P < .001$). Significant differences in FEV₁ were noted immediately after nebulization (median change, 2.0%, 19.0%, 18.1%, 12.4%, and 15.6% for placebo, LEV 0.31 and 0.63, RAC 1.25 and 2.5 mg, respectively; $P < .05$ vs placebo; $P < .05$ for LEV 0.31 and 0.63 vs RAC 1.25 mg). LEV 0.31 mg was the only treatment not different from placebo for changes in ventricular heart rate, QT(c) interval, and glucose ($P > .05$). All active treatments decreased serum potassium (range, -0.3 to -0.6; $P < .002$ vs placebo), and RAC 2.5 mg caused the greatest change ($P < .005$ vs other actives). In a patient subset with severe asthma, a dose-response relationship was observed for levalbuterol, indicating that higher doses were more effective. **CONCLUSION:** LEV was clinically comparable to 4- to 8-fold higher doses of RAC, and it demonstrated a more favorable safety profile. LEV 0.31 mg should be used as the starting dose in 4-11 year old children with mild to moderate persistent asthma. Patients with severe disease might benefit from higher doses.



All values are significantly different than placebo $p < 0.05$



All values are significantly different than placebo $p < 0.05$

Milgrom: 2001

A multicenter, randomized, double-blinded, parallel-group study in children 4-11 years old with mild asthma (FEV1 40%-85% of predicted with $\geq 15\%$ reversibility) to determine safety and efficacy of levalbuterol versus placebo. *Racemic albuterol was included as an active control.* Patients were randomized to receive 21 days of 3 times a day double-blinded treatment with levalbuterol 0.31, 0.63 mg, albuterol 1.25, 2.5 mg or placebo nebulization. 398 patients were enrolled 338 completed the study (approximately 70 per treatment group). Rescue medication were Ventolin MDI and nebulers. *All active treatments produced significant improvement in peak % change in FEV1. There was no evidence of desensitization to either levalbuterol or albuterol at day 21 in comparison to day 0. Increases in HR were similar for 0.63mg of levalbuterol and 1.25 mg of albuterol (4-6 BMP). Albuterol 1.25 mg produced similar or less decrease in serum potassium than levalbuterol 0.63 mg. No significant differences were seen among the treatment groups for asthma symptom assessment score, symptom-free days, and QOL score.*

J Allergy Clin Immunol. 2001 Nov;108(5):726-31.

Comment in: [J Allergy Clin Immunol. 2001 Nov;108\(5\):681-4.](#)

The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients.

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Department of Respiratory Medicine and Allergology, Goteborg University, Goteborg, Sweden.

BACKGROUND: It has been suggested that R-albuterol produces bronchodilation that is comparable with that of racemic albuterol (RS-albuterol) on a 4:1 dose-for-dose basis but systemic side effects on a 2:1 basis, implying better therapeutic ratio for R-albuterol. **OBJECTIVE:** We sought to carefully compare the bronchodilating and systemic effects of R- and RS-albuterol by using a crossover study design. **METHODS:** Twenty asthmatic patients (15.1%-28.7% FEV(1) reversibility) were given R-albuterol (6.25-1600 microg), S-albuterol (6.25-1600 microg), RS-albuterol (12.5-3200 microg), or placebo in a 4 way crossover, double-blind, placebo-controlled fashion. Cumulative doses were given with a Mefar dosimeter, and FEV(1), heart rate, and plasma K(+) levels were measured 20 minutes after each dose. **RESULTS:** Both R- and RS-albuterol produced dose-related improvement in FEV(1) and, at higher doses, increased heart rate and decreased plasma K(+) levels. Neither placebo nor S-albuterol had any significant effect. Individual estimates of the potency ratio for R-albuterol/RS-albuterol were calculated and summarized across all subjects. The geometric mean potency ratio for effects on FEV(1) was 1.9 (95% CI, 1.3-2.8), on HR of 1.9 (95% CI, 1.3-2.9), and on K(+) level of 1.7 (95% CI, 1.3-2.1). **CONCLUSION:** All pharmacologic effects of RS-albuterol reside with the R-enantiomer, and S-albuterol is clinically inactive. The R-albuterol/RS-albuterol potency ratios for local (FEV(1)) and systemic effects (heart rate and K(+)) are similar, suggesting a comparable therapeutic ratio for R-albuterol and RS-albuterol in asthmatic subjects.

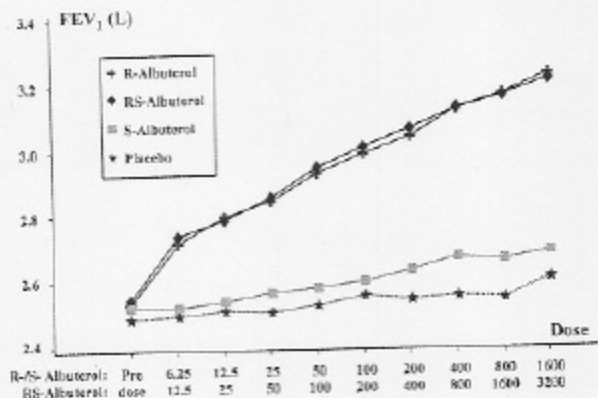
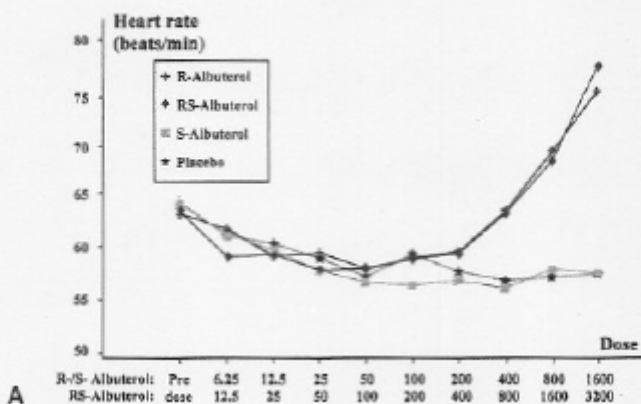


FIG 1. Mean effect of inhaled R-salbuterol (6.25-1600 µg), S-salbuterol (6.25-1600 µg), RS-salbuterol (12.5-3200 µg), and placebo on FEV₁ in 20 patients with mild asthma.



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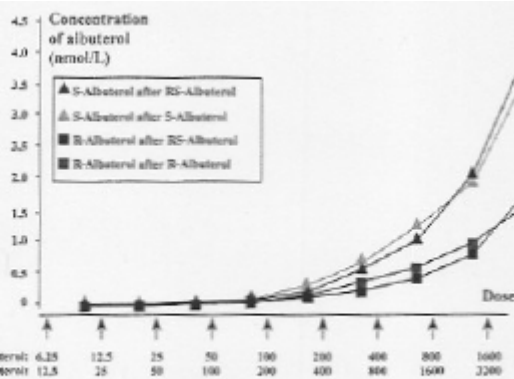


FIG 4. Median plasma concentrations of R- and S-albuterol after inhaled administration of single enantiomer R- or S-salbuterol (6.25-1600 µg) or RS-salbuterol (12.5-3200 µg) in 20 patients with mild asthma.

Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma.

Handley DA, Tinkelman D, Noonan M, Rollins TE, Snider ME, Caron J.

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Albuterol, in all marketed forms, is sold as a racemate, composed of a 50:50 mixture of (R)- and (S)-isomers. Racemic albuterol and the single isomer version (R)-albuterol (levalbuterol) were compared in a randomized, double-blind, *dose-ranging five-way crossover* study in non smoking patients (n = 20) with mild persistent to moderate persistent asthma. Placebo, racemic albuterol (2.50 mg), or levalbuterol (0.31, 0.63, or 1.25 mg) were delivered as single, nebulized doses to 5 male and 15 female nonsmoking patients with asthma aged 18-50 years. Serial pulmonary function was assessed at 15-min intervals and mean time to onset of activity and duration of improvement of forced expiratory volume in 1 sec (FEV1) were measured. In addition, blood chemistries, electrocardiogram (ECG) readings, and patient subjective assessment of adverse symptoms were recorded. Levalbuterol was found to provide significant bronchodilatory activity and was well tolerated. The curves of mean change in FEV1(%) versus time are nearly identical for levalbuterol 1.25 mg and albuterol 2.5. Mean heart rates for levalbuterol 1.25 mg and albuterol 2.5 mg are nearly identical. A dose response curve for levalbuterol was not demonstrated by the data. The proportion of patients experiencing an adverse event, as well as the total number of adverse events reported, was comparable across the five treatment groups.

	Mean Heart Rates					
	Minutes after Nebulization					
	0-30	31-60	61-90	91-120	121-135	136-150
Placebo	80	79	78	78	78	78
Levabuterol 0.31 mg	84*	82*	80	79	76	77
Levabuterol 0.63 mg	84*	82*	80	80	80	77
Levabuterol 1.25 mg	91*	88*	85*	83*	81*	79
Albuterol 2.5 mg	89*	85*	84*	83*	82*	78

Significantly greater than placebo

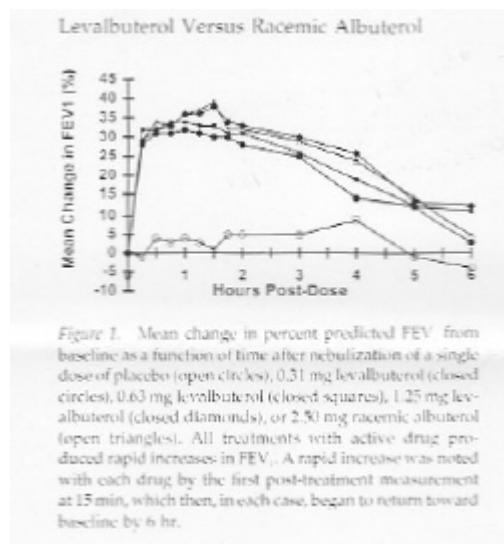


Table 2. Mean Heart Rates

	MINUTES AFTER START OF NEBULIZATION					
	0-30	31-60	61-90	91-120	121-135	136-150
Placebo	80	79	78	78	78	78
Levalbuterol 0.31 mg	84*	82*	80	79	76	77
Levalbuterol 0.63 mg	84*	82*	80	80	80	77
Levalbuterol 1.25 mg	91*	88*	85*	83*	81*	79
Racemic albuterol 2.50 mg	89*	85*	84*	83*	82*	78

*Significantly greater than placebo.

Tolerance to the bronchoprotective effect of beta2-agonists: comparison of the enantiomers of salbutamol with racemic salbutamol and placebo.

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BACKGROUND: Regular use of racemic salbutamol (albuterol) results in the partial loss of its bronchoprotective effect. The 2 enantiomers of salbutamol (albuterol), the bronchodilator R-salbutamol (levalbuterol) and nonbronchodilator S-salbutamol, are now available. **OBJECTIVE:** We sought to compare the effect of regular use of S-salbutamol, R-salbutamol (levalbuterol), racemic salbutamol (albuterol), and placebo on the bronchoprotective effect of a single dose of racemic salbutamol against methacholine-induced bronchoconstriction. **METHODS:** Eleven of 13 well-controlled beta2-agonist-free asthmatic subjects completed a double-blind, placebo controlled, 4-way, randomized, cross-over study comparing racemic salbutamol 2.5 mg, S-salbutamol 1.25 mg, R-salbutamol 1.25 mg, and diluent placebo nebulized and inhaled 3 times daily for 6 days (\geq 6-day washout period). Ten to 12 hours after the last dose, the subjects performed measurement of FEV₁, methacholine PC₂₀, and a repeat methacholine PC₂₀ done 1 hour after the first methacholine test and 10 minutes after 2 puffs (200 microgram) of racemic salbutamol administered from a metered-dose inhaler. The primary endpoint was the methacholine PC₂₀ dose shift (Deltalog PC₂₀/log 2) from before to after administration of 200 microgram of racemic salbutamol. **RESULTS:** The methacholine dose shift was 3.2 doubling doses (9-fold increase in methacholine PC₂₀ after 200 microgram of racemic salbutamol) during the placebo treatment and was unaltered (3.2) after administration of S-salbutamol. The dose shift was significantly lower after both the R-salbutamol and racemic salbutamol treatments (2.2 and 2.6 doubling doses, respectively); there was no significant difference between R-salbutamol and racemic salbutamol. There was no treatment effect on baseline FEV₁, baseline methacholine PC₂₀, or bronchodilation. **CONCLUSION:** Regular treatment with racemic salbutamol or R-salbutamol (levalbuterol), but not S-salbutamol, results in a partial loss of bronchoprotection, without loss of bronchodilation, compared with placebo. **Note:** This study shows that S-albuterol is inert and does not impact the efficacy of albuterol or increase airway hyperresponsiveness.

The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients.

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BACKGROUND: Limited dose-response information is available for nebulized beta2-agonists, especially in young children. **OBJECTIVE:** The purpose of this study was to determine the safety and efficacy of increasing doses of nebulized levalbuterol (Xopenex; the pure R-isomer of racemic albuterol) and racemic albuterol compared with placebo in the treatment of asthma in pediatric patients. **METHODS:** In this randomized, double-blind, single dose, crossover study, children (aged 3 to 11 years) with asthma (resting FEV1 50% to 80% of predicted normal [Polgar's] values) were treated with either levalbuterol, racemic albuterol, or placebo. Eligible subjects underwent a screening visit followed by 4 treatment visits. At each treatment visit, serial pulmonary function tests were completed before and after the treatment; plasma was collected to determine enantiomer levels, and safety was evaluated. **RESULTS:** Five 3- to 5-year-old patients and twenty-eight 6- to 11-year-old patients completed the study, and a total of 87 doses of levalbuterol were administered. In the 6- to 11-year-old group, all doses of levalbuterol were significantly greater than placebo in peak change and percent peak change in FEV1 and area under the FEV1 versus time curve ($P < .05$). The FEV1 values over the 8-hour study period were similar for levalbuterol 0.31 and 0.63 mg and racemic albuterol 2.5 mg and were greatest after levalbuterol 1.25 mg. Median plasma levels of R-albuterol depended on dose and were 0.4, 0.7, 1.2, and 1.0 after levalbuterol 0.31 mg, 0.63 mg, and 1.25 mg and racemic albuterol 2.5 mg, respectively. All patients in the 2.5-mg racemic albuterol arm had measurable plasma levels of S-albuterol, although S-albuterol levels were undetectable in most patients in the levalbuterol arms. In a few patients who received levalbuterol, S-albuterol levels were detected, which was likely because of the use of racemic albuterol as a concomitant medication. All active treatments were well tolerated. beta-Mediated changes in heart rate, potassium, and glucose were dose dependent for all active treatment groups. **CONCLUSION:** *The mean peak change in FEV1 and peak % change in FEV1 versus placebo was statistically different from placebo for all groups. No significant difference in bronchodilator effect could be demonstrated between any of the active regimen. The AUC FEV1 versus placebo was statistically different from placebo for all groups except albuterol 1.25 mg. No significant differences across treatment groups were seen in the incidence of total adverse effects. Changes in potassium and HR were the same for levalbuterol 0.63 versus albuterol 1.2 meq/l. The placebo group had a >15% increase in the mean change in FEV1 which makes the study results questionable.*

	Levalbuterol				Albuterol		
	0.16 mg	0.31 mg	0.63 mg	1.25 mg	1.25 mg	2.5 mg	Placebo
Mean Change FEV1 (L)	0.39*	0.42*	0.41*	0.51*	0.35*	0.40*	0.37
Peak % Mean Change FEV1	28.7*	30.6*	31.1*	36.8*	24.6*	27.9*	26.2
Glucose (mg/dl)	14.6	-0.5	21.2	30.5	16.2	19.6	5.9
Potassium (meq/L)	-0.2	-0.2	-0.5	-0.5	-0.4	-0.6	-0.1
Ventricular Heart Rate (bpm)	0.4	6	10.8	15.9	10.6	10.2	-0.1

* $p < 0.05$ Versus placebo, No significant difference in bronchodilator effect could be demonstrated between any of the active regimen

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Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma.

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BACKGROUND: Racemic albuterol is an equal mixture of (R)-albuterol (levalbuterol), which is responsible for the bronchodilator effect, and (S)-albuterol, which provides no benefit and may be detrimental. **OBJECTIVE:** We sought to compare 2 doses of a single enantiomer, levalbuterol (0.63 mg and 1.25 mg), and equivalent amounts of levalbuterol administered as racemic albuterol (1.25 mg, 2.5 mg) with placebo in patients with moderate-to-severe asthma. **METHODS:** This was a randomized, double-blind, parallel-group trial. Three hundred sixty-two patients 12 years of age or older were treated with study drug administered by means of nebulization 3 times daily for 28 days. The primary endpoint was peak change in FEV1 after 4 weeks. **RESULTS:** Mean percent change FEV1 from baseline was significantly higher than placebo in active treatment areas ($P < 0.001$). Clinically significant ($>15\%$ FEV1) were observed for all active treatments initially and at week 4. This improvement was maintained for at least 5 hours. FEV1 was increased to 81-85% of predicted by both albuterol and levalbuterol. Patients in all of the active treatment arms used significantly less rescue medication when compared with the placebo group. Significant, dose related increases in mean ventricular heart rate relative to predoses values were observed at week 4 after dosing with all active treatment arms in comparison with placebo ($P \leq 0.001$). Statistically significant increases in mean serum glucose occurred in all active treatment arms when compared to placebo. The study was powered to determine differences between active treatments compared with placebo and was not designed to detect inter-treatment differences.

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Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers.

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The pharmacokinetics and pharmacodynamics of inhaled albuterol given as single or multiple doses of racemate (RS-) or single enantiomers (R-, S-) were determined. In an open-label, three-way crossover, parallel-dose study, 1.25 and 5 mg of (R)- and (S)-albuterol and 2.5 and 10 mg of (RS)-albuterol were given via nebulization to 15 healthy volunteers. The pharmacokinetic parameters of each enantiomer were determined by noncompartmental and model-fitting analyses. Both (R)- and (S)-albuterol showed rapid absorption and biexponential decline, with half-lives ($t_{1/2}$) averaging 4 and 6 hours, respectively. There were no differences in pharmacokinetics of (R)-albuterol when administered as (R)- or (RS)-albuterol at the 5-mg dose with equivalent relative bioavailability as seen from maximum concentration (C_{max}) and area under the concentration-time curve (AUC). The same was true for (S)-albuterol at the 1.25-mg and 5-mg doses. The data from 5-mg doses were considered to be more reliable due to assay sensitivity limitations, and indicated equivalent absorption and disposition of the individual enantiomers. There was no evidence of in vivo racemization, and (R)-albuterol did not interconvert to (S)-albuterol. Plasma potassium, plasma glucose, heart rate, and QTc interval were used in linear and Emax models to assess responses relating to (R)-albuterol concentrations. The Emax for potassium change was 1.32 meq/L, with an EC50 of 0.59 and 0.94 ng/mL after administration of (R)- and (RS)-albuterol, respectively. The slopes and intercepts for glucose and heart rate changes were similar after administration of (R)- and (RS)-albuterol. No concentration-effect relationships were evident for QTc interval or for (S)-albuterol. The extrapulmonary responses of (R)-albuterol and adverse effects were similar for single R-enantiomer or the racemic mixture. *There was no significant difference in the pharmacokinetics of R albuterol when administered as R or RS albuterol with equivalent relative bioavailability as seen for maximum concentration and AUC. The same was true for S albuterol. R albuterol did not interconvert to S albuterol. The change in plasma potassium, glucose, and heart rate were similar for single R enantiomer or the racemic mixture at equivalent doses. S albuterol did not have an effect on glucose, heart rate, or potassium. QTc interval was not affected by any study medication. Grant from Sepracor*

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Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine.

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BACKGROUND: Commercially available salbutamol is a racemic mixture consisting of equal amounts of the two enantiomers, R-salbutamol and S-salbutamol, felt to be active and inert, respectively. **METHODS:** A double blind, randomised, four way, crossover study was performed in 12 well controlled asthmatic subjects (forced expiratory volume in one second (FEV1) > 70% predicted, no beta 2 agonists for > or = 4 weeks). Subjects were studied on four days at intervals of 48 hours to seven days. FEV1 was assessed before and both FEV1 and methacholine PC20 were measured 20 and 180 minutes after a single dose of nebulised racemic salbutamol 2.5 mg, R-salbutamol 1.25 mg, S-salbutamol 1.25 mg, and placebo. **RESULTS:** Equivalent bronchodilation was seen for both R-salbutamol and racemic salbutamol (mean (SE) 12.4 (3.1)% and 12.0 (3.0)%, respectively, at 20 minutes and 5.9 (2.9)% and 5.2 (2.2)% at 180 minutes). The increase in FEV1 of 5.2 (0.9)% at 20 minutes and the decline in FEV1 of 2.9 (2.1)% at 180 minutes after S-salbutamol were not significantly different from the placebo response. Compared with placebo the methacholine PC20 after R-salbutamol and racemic salbutamol improved by 3.3 (95% CI 2.5 to 4.1) and 3.4 (95% CI 2.6 to 4.2) doubling doses, respectively, at 20 minutes and 1.2 (95% CI 0.6 to 1.8) and 1.0 (95% CI 0.2 to 1.8) doubling doses at 180 minutes. S-salbutamol resulted in an improvement of 0.9 (95% CI 0.3 to 1.5) doubling doses at 20 minutes and no change at 180 minutes. Restlessness (n = 11) and increased pulse were seen 20 minutes after racemic and R-salbutamol but not S-salbutamol or placebo, and not at 180 minutes. There were no other adverse events. **CONCLUSION:** A single dose of 1.25 mg nebulised R-salbutamol produced equivalent bronchoprotection, bronchodilation, restlessness, and tachycardia as did 2.5 mg of racemic salbutamol. S-salbutamol 1.25 mg had a weak bronchoprotective effect; this could be because of a small amount of contamination with R-salbutamol or because S-salbutamol is an intrinsically weak beta 2 receptor stimulant.