Drug Class Review

Quick-relief Medications for Asthma

Final Update 1 Report
Evidence Tables

October 2008

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The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report based on the information contained in the scan. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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Evidence Table 1. Included studies

Berger, 2006 **Quality rating:** Poor

Design:

Study design RCT DB **Run-in:** 1-week SB **Setting:** Clinic
Country: USA

Sample: # Screened / Eligible / Enrolled
NR / 173/ 150

Withdrawn / Lost to follow-up / Analyzed
16/ NR/134

Inclusion criteria: Children aged 4-11 years; stable asthma for at least 6 months before screening; FEV between 45% and 80% predicted with ≥ 12% reversibility to 2.5 mg of nebulized racemic albuterol at screening

Exclusion criteria: Participation in an investigational study within 30 days of screening; known sensitivity to study medications or components; hospitalization for asthma within 60 days prior to screening; clinically significant upper or lower respiratory tract infection within 2 weeks of screening; clinically significant ECG abnormalities

Comments

Intervention:

Duration: 28 days

Drug name	Dosage	N	Mean age (years)	Gender
Levalbuterol HFA MDI	90µg (2 puffs, 45µg/puff) qid	76	8.3	49% male
Placebo HFA MDI		35	8.1	22% male
Racemic albuterol HFA MDI	180µg (2 puffs, 90µg/puff) qid	39	8.6	23% male

Outcomes:

Effectiveness Outcomes:

Symptoms: NR

Change in treatment regimen for the exacerbation:

	Levalbuterol	Racemic Albuterol	Placebo
LS mean change ± SD in rescue medication usage (days/week)	0.72 ± 0.17*	0.62 ± 0.24*	0.35 ± 0.24
LS mean number ± SD of nebules/day	-0.15± 0.05	-0.05± 0.07	0.14 ± 0.07
Mean ± SD number of asthma control days/week	5.45 ± 1.58	5.76 ± 1.23	4.98 ± 1.88

*P <0.001 levalbuterol vs. placebo; P <0.01 racemic albuterol vs. placebo

Healthcare utilization:

Quality of life

No clinically meaningful differences between the active treatments and placebo for the : Pediatric Asthma QOL Questionnaire, the Child Health Questionnaire, or the patient and physician overall evaluations (data not reported)

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	Levalbuterol n (%)	Racemic Albuterol n(%)	Placebo n (%)
Any adverse event	33(43.4)	22(56.4)	18(51.4)
Discontinued due to AEs	1(1.3)	1(2.6)	3(8.6)
Potentially related AEs	6(7.9)	6(15.4)	5(14.3)
β- mediated AEs	1(1.3)	1(2.6)	1(2.9)
Respiratory AEs	21(27.6)	16(41.0)	12(34.2)
Asthma AEs	8(10.5)	5(12.8)	5(14.3)

Evidence Table 1. Included studies

Chakraborti, 2006 **Quality rating :** Fair

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital clinic
Country: India

Sample: # Screened / Eligible / Enrolled
NR / NR/ 60

Withdrawn / Lost to follow-up / Analyzed
NR/ NR/ 60

Inclusion criteria: Children between 5-15 years of age; mild to moderate acute exacerbation of asthma who were able to perform spirometry

Exclusion criteria: Severe acute exacerbation; coexisting cardiac or renal disease; known intolerance to salbutamol or ipratropium bromide; glaucoma, urinary retention and children who had used oral bronchodilator in the last 12 hours or inhaled bronchodilator in the last 6 hours

Comments Patients could be enrolled twice in study if events were more than one month apart

Intervention:

Duration: 30 minutes

Drug name	Dosage	N	Mean age	Gender
Salbutamol with ipratroprium bromide*	100 µg /actuation of salbutamol; 20µg ipratropium	30	106 months	63% males
Salbutamol*	100 µg /actuation	30	118 months	57% males

*All patients were administered 4 actuations of salbutamol through similar looking MDI and spacer. Then 4 actuations of either ipratropium or placebo were administered

Outcomes:

Effectiveness Outcomes:

Symptoms

Comparison of salbutamol with ipratropium bromide and salbutalmol after treatment

	Salbutamol with ipratropium	Salbutamol	p-value
Heart rate/min	119.43±17.09	115.3±18.70	0.38
Respiratory rate/min	27.9±4.67	28.97±5.84	0.44
Wheeze score	1.07±0.83	1.2±0.71	0.51
Accessory muscle score	0.17±0.46	0.43±0.82	0.24

Change in treatment regimen for the exacerbation: NR
Healthcare utilization: NR
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

NR

Evidence Table 1. Included studies

Hamilos, 2007 **Quality rating:** Poor

Design:

Study design RCT Open **Run-in:** 1-week SB **Setting:** NR **Country:** USA

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
NR / 932 / 746	330/ 40 /746

Inclusion criteria:

≥ 12 years; had stable asthma for at least 6 months; an FEV_1 of 50% or higher and 80% or lower of predicted, 12% or higher of reversibility of airflow obstruction within 13 to 30 minutes after administration of 180µg of racemic albuterol MDI; used a β_2 - adrenergic agonist, antiasthma anit-inflammatory medication, or over-the-counter asthma medication for at least 6 months before screening

Exclusion criteria: History of life-threatening asthma within 3 months of screening or if they were hospitalized for acute asthma within 45 days of screening; greater than 10-pack-year history of cigarette smoking within 6 months of screening

Comments * The study protocols were amended to reduce the study period to 6 mos for newly-enrolled patients. 7% of patients were from prior phase 3 trials with no reason given

Intervention:

Duration: 6 months to 1 year

Drug name	Dosage	N	Mean age	Gender
Levalbuterol	MDI 90ug qid	496	38	35.3% male
Racemic albuterol	MDI 180ug qid	250	39	33.2% male

Outcomes:

Effectiveness Outcomes:

Symptoms: NR

Healthcare utilization: NR

Asthma Quality of Life Questionnaire (AQLQ)

Both groups improved to a similar extent on the adult AQLQ.
Pediatric AQLQ was greater for levalbuterol than racemic albuterol:
levalbuterol 0.96±0.92; racemic albuterol -0.02+1.18

	Levalbuterol	Racemic Albuterol
Compliance Rate (12 months; %)	95.70%	96.10%
Rescue Medication Use	72.60%	68.90%

Mortality: 0

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

No. (%) of patients

	Levalbuterol	Racemic albuterol
Adverse events		
Body as a whole	180 (36.3)	104 (41.6)
Abdominal pain	18 (3.6)	17 (6.8)
Unintentional injury	37 (7.5)	26 (10.4)
Flu syndrome	19 (3.8)	17 (6.8)
Headache	67 (13.5)	38 (15.2)
Pain	48 (9.7)	33 (13.2)
Respiratory system	272 (54.8)	141 (56.4)
Asthma	91 (18.3)	49 (19.6)
Bronchitis	36 (7.3)	18 (7.2)
Cough increased	40 (8.1)	24 (9.6)
Pharyngitis	49 (9.9)	25 (10.0)

Rhinitis	48 (9.7)	39 (15.6)	
Sinusitis	56 (11.3)	31 (12.4)	
Viral infection	150 (30.2)	71 (28.4)	
Overall frequency of Aes (%)	72	76.8	(p = 0.12)
At least 1 adverse event	357 (72.0)	192(76.8)	
Serious adverse events[1]	18 (3.6)	13 (5.2)	
Asthma adverse events			
Overall	91(18.3)	49(19.6)	
No. of single events	70(14.1)	33(13.2)	
Duration > 24 hours	83(16.7)	43(17.2)	
Asthma attack[2]			
Overall	81(16.3)	46(18.4)	
No. of single events	61(12.3)	34(13.6)	
Duration > 24 hours	74(14.9)	41(16.4)	
Expanded - definition asthma adverse events[3]			
Overall	131(26.4)	83(33.2)	
No. of single events	71(14.3)	48(19.2)	
Duration > 24 hours	123(24.8)	77(30.8)	

[1] Serious adverse events included any event that was fatal or life threatening, was permanently disabling, required hospitalization, was a congential anomaly, or required intervention to prevent permanent damage

[2]Defined as an asthma adverse event that required hospitalization, emergency department visit, treatment with oral burst or parentera cortocosteroids, or an unscheduled clinic visit

[3] Defined as adverse events of asthma, combined with adverse events of bronchitis, cough increase, dysponea, or lung disorder

Evidence Table 1. Included studies

Nowak, 2006 **Quality rating:** Fair

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital ED/clinic
Country: USA

Sample: # Screened / Eligible / Enrolled
NR /NR/627

Withdrawn / Lost to follow-up / Analyzed
1/0/626

Inclusion criteria: ≥ 18 years; presented to ED/clinic with acute exacerbation of asthma; an FEV_1 value of 20-55% predicted; at least a 6-month history of physician diagnosed asthma; an oxygen saturation of at least 90% with no more than 6L/min supplemental oxygen; non-pregnant; no other known (non-asthma) cause of wheezing or shortness of breath

Exclusion criteria: Respiratory distress of sufficient severity to preclude enroolment in the trial were excluded to avoid delayed treatment; patients administered therapy other than oxygen after ED/clinic arrival; history of severe asthma within previous 12 months; undergone treatemnt of acute asthma within 2 weeks; or hospitalization within 1 month of presentation; ≥ 10-pack year smoking history

Comments

Intervention:

Duration:

Drug name	Dosage	N	Mean age	Gender
Levalbuterol	1.25 mg	315	37.2	62.2% female
Racemic albuterol	2.5 mg	312	37	61.2% female Note: all patients received 40 mg of prednisone

Both treatment drugs were administered every 20 minutes in the first hour, then every 40 minutes for 3 additional doses, then as necessary for up to 24 hours. All patients received 40 mg prednisone Po.

Outcomes:

Effectiveness Outcomes:

Symptoms: NR
Change in treatment regimen for the exacerbation: NR

Healthcare utilization:	Levalbuterol		Racemic albuterol		
Time to discharge (min)	76		78.5		p= .74
Admission rate (%)	7	(95% CI 4.2-9.8)	9.3	(95%CI 6.1-12.6)	p= .28
Relapse rate (% at 30 days)	5.5		5		p= NR
Blood glucose	NSD		NSD		
Potassium	NSD		NSD		

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	Levalbuterol(%)	Racemic albuterol (%)
Overall	9.80	10.90
Headache	1.00	3.20
Nervousness	3.20	2.20
Tremor	2.20	2.20
Tachycardia	1.9	2.9
Asthma event	4.8	3.5

Evidence Table 1. Included studies

Ralston, 2005 **Quality rating:** Fair

Design:

Study design RCT DB **Run-in:** NA **Setting:** Hospital **Country:** USA

Sample: # Screened / Eligible / Enrolled: 833 / 306/ 154; # Withdrawn / Lost to follow-up / Analyzed: 14/ 0/ 140

Inclusion criteria: Patients 6-18 years; history of asthma of any severity; demonstrated ability to use a peak flow meter and with a PEF of <80% on presentation to ED

Exclusion criteria: Known sensitivity to study meds; previous study enrollment; impending or actual respiratory arrest or treatment or treatment with Levalbuterol or Ipratropium bromide within the 6 h of study enrollment

Comments

Intervention:

Duration: 1 treatment

	Dosage	N	Mean age (years)	Gender
Drug name				
Racemic albuterol and ipratropium bromide	Up to 3 nebulized treatments 1mL (5.0 mg) RAC mixed with 1.25 mL (0.25 mg) IB followed as needed by RAC dosing	76	11.5	50 % male
Levalbuterol	Up to 6 nebulized treatments 3.0 mL (1.25mg) LEV	78	11.7	58% male

Outcomes:

	Racemic albuterol and Ipratropium bromide n (%)	Levabuterol n(%)
Effectiveness Outcomes:		
New symptoms no. (%)		
Tremor	20(29)	17(24)
Nervousness	13(19)	8(11)
Nausea or vomiting	6(9)	2(3)
Palpitations	9(13)	5(7)
Headache	9(13)	6(8)
Any symptoms	33(49)	29(40)
HR_{final} beats/min mean (SE)	126 (3.0)	114(2.7)
HR_{max} beats/min mean (SE)	130 (3.4)	119(3.1)
Increase $HR_{initial\ to\ final}$		
Beats/ min mean (SE)	26(2.8)	10(3.0)
% Median (Q_1, Q_3)	20(13,43)	8(-1,23)
Increase $HR_{initial\ to\ max}$		
Beats/ min mean (SE)	29 (3.1)	16(3.0)
% Median (Q_1, Q_3)	26(14, 48)	9 (2, 27)
HR_{max} above normal range for age # (%)	47(73)	35(51)

Symptoms: NR

Change in treatment regimen for the exacerbation: NR

Healthcare utilization:

	Racemic albuterol and Ipratropium bromide	Levabuterol	p Value
ED length of stay (LOS) min median (Q_1, Q_3)	94(70, 133)	80 (60, 122)	0.13
72 hr return for asthma	0(0)	1(1)	1
Number of adjunctive meds in ED # (%)	9(13)	21(29)	0.022

Oral steroids in ED # (%)	59(87)	50(70)	0.014
i.v. steroids in ED # (%)	0(0)	1(1)	1

Admission rate: admission rate : 1.4% for study population; 2 study patients admitted 1 (RAC/IB) to PICU and 1(LEV) to ED

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

No serious AEs reported

Evidence Table 1. Included studies

Salo, 2006 **Quality rating:** Good

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital ED
Country: USA

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
375 / 166/63	1/ NR/ 62

Inclusion criteria: >18 years; PEFR<70% predicted; prior history of asthma; wheezing; or wheezing for the first time and meeting ATS definition of asthma including patients who had a history of asthma diagnosed by a physician or who had episodes of wheezing that improved with β-2 agonist inhalers

Exclusion criteria: Refusal to give informed consent; use of ipratroprium bromide in the past 48 hours; previous enrollment in this study; greater than 20 pack year history of smoking ; symptomatic angina pectoris; known symptomatic atherosclerotic heart disease;; patients who can perform a PEFR; pregnant women; HR >150 beats per minute, BP> 180/100 mm Hg; cystic fibrosis; tuberculosis or pulmonary malignancies; any infection controlled with antibiotics; pneumonia; active in any study at enrollment or 4 weeks prior; taking any oral steroids; known allergies to study medications; current alcohol or drug use

Comments

Intervention:

Duration: 120 minutes

Drug name	Dosage	N	Median age	Gender
Albuterol and ipratropium bromide*	7.5 mg/h and 1.0 mg/h	33	33	
Albuterol*	A: 7.5 mg/h	30	38	

* Both treatments given continously over 120 minutes

Outcomes:

Effectiveness Outcomes:

Symptoms: NR
Change in treatment regimen for the exacerbation: NR
Healthcare utilization:

Admission rates

Albuterol and ipratropium bromide	8/32 (25%)	OR: 1.66 (95% CI, 0.48 - 5.8) p = 0.621
	5/30 (16.7%)	

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Shortness of breath

Albuterol and ipratropium bromide	1 (3%)
Albuterol	1 (3%)

Mild congestive heart failure

Albuterol	1 (3%)

Evidence Table 1. Included studies

Sharma, 2004 **Quality rating:** Poor

Design:

Study design RCT NB **Run-in:** NR **Setting:** Hospital ED **Country:** India

Sample: # Screened / Eligible / Enrolled: NR/ NR/ 50; # Withdrawn / Lost to follow-up / Analyzed: NR/ NR /50

Inclusion criteria: 6-14 years; reported to ED with acute exacerbation of bronchial asthma

Exclusion criteria: Life threatening or severe attack characterized by cyanosis, silent chest or poor air entry maked by dyspnoea so that a child was unable to speak 3-4 words; PEFR <30% for height; received bronchodilator 6 hours prior to admission; history of previous admission to ICU

Comments Listed refernce did not provide specific wheeze or dypnea score

Intervention:

Duration: 240 minutes

Drug name	Dosage	N	Mean age	Gender
Salbutamol (via nebulizer)	150ug/kg/dose every 20 minutes for 3 doses; maximum 5.0mg dose	25	10.3	NR
Combined salbutamol and ipratropium bromide (via nebulizer)	250 µgm /dose for 3 doses every 20 minutes	25	10.6	NR

Outcomes:

Effectiveness Outcomes:

		Wheeze Score*	*p-value*	Dysponea Score*	*p-value*
Symptoms	Salbutamol (via nebulizer)	0.52±0.1	<0.05	0.60±0.24	<0.05
	Combined salbutamol and ipratropium bromide (via nebulizer)	0.2±0.08	<0.05	0.20±0.08	<0.05

* 240 minutes

Change in treatment regimen for the exacerbation: NR
Healthcare utilization: Hospitalization rate: salbutamol 4/25 (16%) ; salbutamol and ipratropium bromide 1/25 (4%)
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	No. of patients (%)	
	Salbutamol	**Salbutamol and Ipratroipium Bromide**
Tremors	8(32%)	4(16%)
Vomiting	3(12%)	1(4%)
Cough	0	6(24%)
Transient eye irritation	0	2(8%)

Evidence Table 1. Included studies

van der Merwe L, 2006 **Quality rating:**

Design:

Study design: Case-control **Run-in:** N/A **Setting:** Hospital and respiratory clinic
Country: South Africa

Sample: Severe life threatening asthma (SLTA): 30
Control: 60

Inclusion criteria: 13-45 years
SLTA: meet admission criteria for SLTA

Exclusion criteria: < 13 years; > 45 years
Control: history of an asthma related admission to an ICU

Comments: The SLTA group were drawn from patients admitted to the emergency room while the control group was drawn from an outpatient respiratory clinic

Population: **Mean age (SE):** SLTA 31 (1.7); Control 30.8(1.1)
Gender (% female): SLTA 83.3; Control 60

Intervention:

Duration:

Drug name	Dosage	N	Mean age	Gender
Various drugs (includes fenoterol 200 ug MDI)	NR			

Outcomes:

Adverse Events and Comments:

Mortality:
SLTA: 13% (4/30)
Control: NR

Treatment with asthma medications in study patients
β agonists (%) - Inhaled fenoterol*
Cases: 68 (17/25)
Control: 28.8 (17/59)
OR 6(95% CI 2.2 TO 16.2)
p = 0.0004

* Subjects not on fenterol were on salbutamol except for one patient in the SLTA group who was suing inhaled anticholinergic medication

Evidence Table 1. Included studies

Watanasomsiri, 2006 **Quality rating:** Fair

Design:

Study design: RCT DB **Run-in:** NR **Setting:** Hospital
Country: Thailand

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
NR / NR/ 74	3/ 0 / 71

Inclusion criteria: A clinical diagnosis of asthma. Patients < 5 years had to have ≥ 3 episodes of wheezing before the presenting illness and a history of physician diagnosed wheezing.

Exclusion criteria: Patients excluded if they presented with a first-time wheezing episode and if they had 1 or more of the following conditions: coexistent cardiac, renal, or other chronic pulmonary diseases; bronchopulmonary dysplasia;intolerance to salbutamol or ipratroprium bromide; glaucoma; or urinary retention. Patients who had used ipratroprium bromide within 24 hours, used oral corticosteroids within 3 days, and required immediate resuscitation or airway intervention were also excluded from the study

Comments

Population:

Intervention:

Duration: Every 20 minutes for 120 minutes and additional doses of salbutamol every 30 minutes PRN

Drug name:	Dosage	N	Mean age	Gender
Salbutamol mixed with 250 µ of ipratropium bromide (Treatment)	NR	38	7.4 years	NR
Salbutamol mixed with isotonic NaCL solution (Control)	NR	33	6.6 years	NR

Comments: The dose of salbutamol was 1.2 mg for body weight < 10 kg and 2.5 mg for body weight > 10 kg.
All patients received 0.5 mg/kg of an oral steroid with the second dose of nebulized solution

Outcomes:

Effectiveness Outcomes:

Symptoms: Authors reported no statistically significant differences in percent change in clinical scores (Accessory muscle score; Wheeze score; Dyspnea score) were found. Subgroup analysis by age and severity showed no statistically significant differences between the 2 groups at any time point. No baseline or follow-up data reported for clinical scores.

Change in treatment regimen for the exacerbation: NR

Healthcare utilization (%): Treatment 5 (2/38); Control 9 (3/33) were hospitalized

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Headache (%)
Treatment: 3 (1/38)
Control: 0
Nausea (%)
Treatment: 3 (1/38)
Control: 3(1/33)

Evidence Table 1. Included studies

Wraight, 2004 **Quality rating:** Fair-poor

Design:

Study design RCT NR Parallel **Run-in:** 2 weeks **Setting:** **Country:** New Zealand

Sample: # Screened / Eligible / Enrolled 47 / 40/ 40 # Withdrawn / Lost to follow-up / Analyzed 9/ NR / 31

Inclusion criteria: 18-70 years, taking a minimum of 200 µ/day of inhaled beclomethasone or equivalent; methacoline PD < 8 µmol; and non-smokers or ex-smokers (< 5 pack-years).

Exclusion criteria: History of life-threatening asthma; a requirement for oral prednisone within the previous 3 months; inability to withdraw short or long-acting beta agonists; and any other significant medical conditions.

Comments The 2-week run-in period withdrew all beta-agonist treatment from patients and substituted ipratropium bromide as the sole reliever medication.

Intervention:

Duration: Phase 1: 2 weeks; Phase 2: continued until a deterioration in asthma control (LOC) occurred after inhaled corticosteroid therapy (ICS) withdrawal.

Drug name	Dosage	N	Mean age	Gender
Salbutamol/ Ipratropium	100 µg/20 µg, 4 puffs tid	18	41.2	39 % male 61 % female
Ipratropium	20 µg, 4 puffs tid	18	39.8	56% male 44% female

Outcomes:

Effectiveness Outcomes:

Symptoms: Mean time to loss of asthma control (days): Salbutamol/Ipratropium 8.9 (14.5 to 13.3); Ipratropium 16.8 (12.2 to 21.4) p = .03
Change in treatment regimen for the exacerbation:
Healthcare utilization: NR
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Unstable asthma	1 (2.5%)
Required β-agonist	1(2.5%)
Inadequate rise in eNO	5(12.5%)

Evidence Table 2. Quality assessment of controlled trials for quick relief medications for asthma

Internal validity

Author Date Country	Was the assignment to the treatment groups really random?	Was the treatment allocation concealed?	Were the groups similar at baseline in terms of prognostic factors?	Were the eligibility criteria specified?	Were outcome assessors blinded to the treatment allocation	Was the care provider blinded?	Was the patient kept unaware of the treatment received	Did the article include an ITT analysis, or provide the data needed to calculate it?	Did the study maintain comparable groups?
Berger, W 2006 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	Unclear; reported as DB	Unclear; reported as DB	Yes	Yes (5/150 patients excluded)	Yes
Chakraborti, A 2006 India	Yes	Yes (3rd party administration of MDIs)	Yes (salbutaomol group 12m older, p=0.04)	Yes	Yes	Yes	Yes	Unclear; attriton NR	Unclear
Hamilos, D 2007 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	No	No	No	Unclear	Unclear
Nowak, R 2006 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	Unclear; reported as DB	Unclear; reported as DB	Unclear	Yes (Table 2 accounts for 626/627 subjects)	Yes
Ralston, M 2005 USA	Yes (random number table)	Yes (central randomization)	Yes	Yes	Yes	Yes	Yes	No (completers only analyzed, 90.9% of total)	Yes
Salo, D 2006 USA	Yes (random number table)	Yes (central randomization)	Yes	Yes	Unclear; reported as DB	Yes (treatments were identical)	Yes (treatments were identical)	Yes; 62/63 randomized were analyzed	Yes
Sharma, A 2004 India	Unclear, methods NR	Unclear, methods NR	Yes	Yes	No, open label	No, open label	No, open label	Unclear; appears that all subjects were analyzed; no correction of multiple comparisons	Yes
Watanasomsiri, A 2006 Thailand	Unclear, methods NR	Yes (central randomization and dispensing by 3rd party)	No, are statistical differences in SaO2 and time of onset of attack between groups; SaO2 differered by 1.3%	Yes	Yes	Yes	Yes	No, 71/74 were analyzed	Yes
Wraight 2004 New Zealand	Unclear, methods NR	Unclear, methods NR	Yes, groups were statistically the same but FEV1 was greater in the IB group; post hoc analysis with matching on FEB1 was therefore performed.	Yes	Unclear; no mention blinding	Unclear; no mention blinding	Unclear; no mention blinding	No; appears that only completers were analyzed (31/40)	Unclear; FEV1 differed at baseline (P>0.05)

Evidence Table 2. Quality assessment of controlled trials for quick relief medications for asthma

				External validity					
Author Date Country	**Did the article report attrition, crossovers, adherence, and contamination?**	**Was there important differential loss to follow-up or overall high loss to follow-up?(give numbers in each group)**	**Quality**	**How similar is the population to the population to whom the intervention would be applied?**	**How many patients were recruited?**	**What were the exclusion criteria for recruitment? (Give numbers excluded at each step)**	**What was the funding source and role of funder in the study?**	**Did the control group receive the standard of care?**	**What was the length of follow-up? (Give numbers at each stage of attrition)**
Berger, W 2006 USA	Yes No No No	No	Fair	Unclear; 150/173 patients randomized	Unclear; NR for run-in period; 173 started run-in	NR	Sepracor Inc; role NR; 2 coauthors are from Sepracor	No, qid regular dosing of albuterol is not usual care	28 days
Chakraborti, A 2006 India	No No No No	Unclear	Fair	Unclear; recruitment NR	NR	Severe asthma; comorbid conditions	NR	Yes (albuterol)	Outcomes measured "after treatment" but time interval NR
Hamilos, D 2007 USA	Yes No Yes No	High loss to F/U (44% (similar rates between groups); authors amended protocol from 12 to 6-m F/U and defined completion with respect to 6 months; no rationale for change given	Poor	Unclear 746/932 enrolled	932/ accessi ble popuolation NR	Recent, severe asthma attack	Sepracore Inc.; role NR; 4 coauthors from Sepracor		52 weeks
Nowak, R 2006 USA	No No No No	Unclear; appear to have only lost 1 patient (table 2) but did use LOCF for FEV1 data	Fair	Unclear; total accessible population NR	Unclear; 627 entered study	Severe respiratory distress	Sepracor Inc; role NR	Yes	24 hours
Ralston, M 2005 USA	Yes No No No	No	Fair	Unclear; only 154/833 elegible patients were recruited	154	impending respiratory arrest, treatmen with levalbuterol or IB in last 6h	NR: site of study was Naval Medical Center, Portsmouth, Virginia	Yes	Length of ER visit
Salo, D 2006 USA	Yes Yes No No	No	Good	Unclear; 66/375 were enrolled	66	92/375 potential patients were 'missed' for inclusion; exclusion criteria: use of IB in last 48h and others	Funder NR; B&B Technologies supplied the Hope Nebulizers for the study	Yes (continuous albuterol)	Length of ER visit
Sharma, A 2004 India	Unclear No No No	Unclear	Poor	Unclear	MR	Exclusion criteria NR	NR	Yes (albuterol)	240 minute (ER visit)
Watanasomsiri, A 2006 Thailand	Yes No No No	No	Fair	Unclear; recruitment NR	NR	First-time wheezers, other comorbidities, etc	NR	Yes (albuterol)	Length of ER visit
Wraight 2004 New Zealand	Yes No Yes No	No; 5 patients withdrawn as failed to demonstrate a significant increase in airway inflammation after withdrawal of steroids	Fair-poor	Unclear (recruitment NR)	47 were screened	Severe asthma, recent oral steroids		No, both groups received regular SABA and steroids were withdrawn from both groups	Phase 1 was 2 weeks; phase 2 until loss of control; longest time to loss of control NR