Drug Class Review
on
Beta$_2$-Agonists

Final Report Evidence Tables

November 2006

The Agency for Healthcare Research and Quality has not seen or apporved this report

A literature scan of this topic is done periodically.

Note: This report has been superseded by the *Controller Medications for Asthma* and *Quick-relief Medications for Asthma* reports

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to supersede this report. The updated versions of the report are Quick Relief Medications for Asthma finalized in October 2008 and Controller Medications for Asthma finalized in November 2008

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EVIDENCE TABLES

Funding:

The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

Evidence Table 1. Systematic reviews of beta-agonists: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: population
Salpeter 2006	To assess the effect of LABA on severe asthma exacerbations	1966-12/2005	RCTs of LABA lasting ≥ 3m	19 trials; 33,826 patients followed for 16,848 patient-years	Mean duration 6.0m	Mean age placebo group: 37.7 (SD 4.7)y % female placebo group: 49.8 Use of inhaled steroids placebo group: 53.2% 15% African American

Evidence Table 1. Systematic reviews of beta-agonists: data

Author Year	Characteristics of identified articles: interventions	Results	Conclusions
Salpeter 2006	Use of LABA All allowed use of SABA	**Hospitalizations** OR: LABA vs placebo: 2.6 (95% CI, 1.6 to 4.3) overall; children 3.9 (CI, 1.7 to 8.8); adults 2.0 (1.0 to 3.9) (between-group p-value 0.22) Risk difference: 0.7% (CI, 0.1 to 1.3%) overall Subgroup analyses: salmeterol: OR 1.7 (CI, 1.1 to 2.7); formoterol 3.2 (CI, 1.7 to 6.0) (between-group p-value 0.109) **Life-threatening asthma exacerbations** OR: LABA vs placebo: 1.8 (1.1 to 2.9) Risk difference: 0.12% (CI, 0.1 to 0.3%) NSD between adults and children and salmeterol and formeterol **Asthma-related deaths** 14 trials reported data SMART trial: OR 3.5 (CI, 1.3 to 9.3) All trials with and without deaths: risk difference 0.07% (CI, 0.01 to 0.1)	LABA increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths; risks are similar with salmeterol and formoterol and in children and adults; concomitant inhaled steroids do not adequately protest against these AEs

Evidence Table 2. Systematic reviews of beta-agonists: quality assessment

Internal Validity

Author Year	Clear review question	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?
Salpeter 2006	Yes	Yes	Yes	No	Yes	Yes

Evidence Table 2. Systematic reviews of beta-agonists: quality assessment

Author Year	Internal Validity: Standard method of appraisal of studies?	Internal Validity: Exclusion criteria	Quality	Funding source and role of funder
Salpeter 2006	Yes	Yes	Good	NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Campbell, 1999; Campbell, 2000 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT Open Crossover **Run-in :** 7-14 days days **Setting:** Community practice

Country: UK

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	600 /	469	NR /	NR /	460

Inclusion criteria:

A documented diagnosis of asthma and have been receiving at least 200 ug day inhaled steroid at a constant dose for at elast 4 weeks prior to entering the study. In addition the patients must have been using a SABA as required and in the opinion of the i

Exclusion criteria:

Significant disease past or present or clinically relevant laboratory result which would interfere with the study; documented or suspected diagnosis of irreversible chronic airways obstruction; PEF <50% of predicted, a respiratory tract infection within

Comments:

Patients were required to demonstrate an increase in PEF from before to after inhalation of a short acting beta agonist which was equal to or greater than 15% or an increase which is equal to or greater than 9% of predicted normal either documented in the

Population: **Mean age:** 40.2 years

Gender: NR% Female

Intervention:

Duration: 8 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug BID	24ug	460	40.3 years	59.78% Female
Salmeterol 50ug BID	100ug	231	NR	NR
Salmeterol 50ug BID	100ug	229	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, morning

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
NR NR(NR)	NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)	NR NR(NR)
28.9(NR)	19.9(NR)	26.1(NR)

PEF, evening

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
227 367.3(94.5)	115 375.4(102.6)	107 362.1(94.3)
227 NR(NR)	115 NR(NR)	107 NR(NR)
21.1(43.7)	15(42.2)	25.8(53.9)

Formoterol 12ug vs Salmeterol 50ug Accuhaler, p value: 0.29

Formoterol 12ug vs Salmeterol 50ug pMDI, p value: 0.41

Salmeterol 50ug Accuhaler vs Salmeterol 50ug pMDI, p value: 0.11

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Campbell, 1999; Campbell, 2000 Quality rating (Efficacy, Safety): Fair, Fair

Effectiveness Outcomes:

Patients with hospital admits or visits to A&E

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
230 NR(NR)	119 NR(NR)	111 NR(NR)
230 1(4)	119 1(7)	111 2(15)
NR(NR)	NR(NR)	NR(NR)

Daytime asthma symptoms

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
230 NR(NR)	119 NR(NR)	111 NR(NR)
NR NR(NR)	NR NR(NR)	NR NR(NR)
-0.54(NR)	-0.35(NR)	NR(NR)

Formoterol 12ug vs Salmeterol 50ug Accuhaler, p value: 0.014

Notes: Formoterol vs salmeterol accuhaler p=0.014; NSD between Formoterol and salmeterol MDI or between the 2 salmeterol groups

Nights/week of undisturbed sleep at 8w

NR NR(NR)
NR NR(NR)
NR(NR)

Notes: All groups increased by 1-1.5 nights/week; NSD between groups

No. of patients with worsening of asthma

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
230 NR(NR)	119 NR(NR)	111 NR(NR)
230 26(11)	119 14(12)	111 13(12)
NR(NR)	NR(NR)	NR(NR)

% of days symptom-free and use no bronchodilator

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
230 NR(NR)	119 NR(NR)	111 NR(NR)
228 32.8(2.3)	118 24.1(2.6)	108 28.0(3.2)
NR(NR)	NR(NR)	NR(NR)

Formoterol 12ug vs Salmeterol 50ug Accuhaler, p value: 0.02

Formoterol 12ug vs Salmeterol 50ug pMDI, p value: 0.21

Notes: The differences between treatments were not statistically significant

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Campbell, 1999; Campbell, 2000 **Quality rating (Efficacy, Safety): Fair, Fair**

Adverse Events:

Pain

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
460 NR(NR)	231 NR(NR)	229 NR(NR)
422 71(17)	217 21(10)	209 28(13)
NR(NR)	NR(NR)	NR(NR)

Central and peripheral nervous

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
460 NR(NR)	231 NR(NR)	229 NR(NR)
422 44(10)	217 19(9)	209 17(8)
NR(NR)	NR(NR)	NR(NR)

Respiratory system disorders, total

Formoterol 12ug	Salmeterol 50ug Accuhaler	Salmeterol 50ug pMDI
460 NR(NR)	231 NR(NR)	229 NR(NR)
422 167(40)	217 94(43)	206 89(43)
NR(NR)	NR(NR)	NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1994 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Crossover **Run-in :** 48 hrs days **Setting:** NR
Country: Italy

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	16	0	0	16

Inclusion criteria:

Fulfilled American Thoracic Society criteria for chronic bronchitis, were non-atopic, were heavy smokers (between 40.3 and 72.8 pack years) but had not smoked cigarettes within the preceeding 4 months, had had no change in symptom severity or treatment i

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 64.3 years
Gender: 0% Female

Intervention:

Duration: Single dose, over 8 non-consecut

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 24ug	single dose	16	64.3 years	0% Female
Salmeterol 50ug	single dose	16	64.3 years	0% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 50ug		Salmeterol 50ug	
16	1.13(1.04)	16	1.04(1.24)
16	1.5(NR)	16	1.31(NR)
	0.37(NR)		0.27(NR)

Formoterol 50ug vs Salmeterol 50ug, p value: >0.05

FEV1, maximum

Formoterol 50ug		Salmeterol 50ug	
16	1.13(1.04)	16	1.04(1.24)
16	1.53(NR)	16	1.38(NR)
	0.4(NR)		0.34(NR)

FEV1, mean time of onset, increase at least 15%

Formoterol 50ug		Salmeterol 50ug	
16	NR(NR)	16	NR(NR)
16	652(NR)	16	652(NR)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1994 — Quality rating (Efficacy, Safety): Fair, Fair

Effectiveness Outcomes:

Onset of action

Formoterol 50ug		Salmeterol 50ug	
16	NR(NR)	16	NR(NR)
16	3min 56 s	16	10min 8 sec
	NR(NR)		NR(NR)

Formoterol 24ug vs Salmeterol 50ug, p value: <0.05

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

The HR & BP did not change significantly during the tests.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1995 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** Community practice
Country: Italy

Sample: # Screened / Eligible / Enrolled: NR / NR / 12 — # Withdrawn / Lost to follow-up / Analyzed: 0 / 0 / 12

Inclusion criteria:

Fulfilled American Thoracic Society criteria: i.e. they were current or former smokers without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnea when walking quietly on level ground, or both, were

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 62.6 years
Gender: 0% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	single dose	12	62.6 years	0% Female
Formoterol 24ug	single dose	12	62.6 years	0% Female
Formoterol 36ug	single dose	12	62.6 years	0% Female
Salmeterol 25ug	single dose	12	62.6 years	0% Female
Salmeterol 50ug	single dose	12	62.6 years	0% Female
Salmeterol 75ug	single dose	12	62.6 years	0% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FEV1

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 0.58(0.22)	12 0.58(0.22)	12 0.58(0.22)	12 0.58(0.22)	12 0.58(0.22)	12 0.58(0.22)
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1995 **Quality rating (Efficacy, Safety): Fair, NA**

FVC

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FEV1

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 0.58(0.21)	12 0.58(0.21)	12 0.58(0.21)	12 0.58(0.21)	12 0.58(0.21)	12 0.58(0.21)
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FEV1 at least 160ml increase, no. of pts

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 8(67)	12 8(67)	12 9(75)	12 4(33)	12 6(50)	12 6(50)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FEV1 at least 25% increase, no. of pts

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 10(83)	12 10(83)	12 9(75)	12 6(50)	12 5(42)	12 6(50)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FEV1 at least 15% increase, no. of pts

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 11(92)	12 10(83)	12 11(92)	12 8(67)	12 12(100)	12 11(92)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

FVC

Formoterol 12ug	Formoterol 24ug	Formoterol 36ug	Salmeterol 25ug	Salmeterol 50ug	Salmeterol 75ug
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)	12 NR(NR)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1995 — Quality rating (Efficacy, Safety): Fair, NA

FEV1

Formoterol 12ug		Formoterol 24ug		Formoterol 36ug		Salmeterol 25ug		Salmeterol 50ug		Salmeterol 75ug	
12	0.58(0.21)	12	0.58(0.21)	12	0.58(0.21)	12	0.58(0.21)	12	0.58(0.21)	12	0.58(0.21)
12	NR(NR)	12	NR(NR)	12	NR(NR)	12	NR(NR)	12	NR(NR)	12	NR(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

All FEV1 data were not reported, shown in the graphs only.
The maximum increase in FEV1 over baseline values occurred
- formoterol: 1h after inhalation
- salmeterol: 2h after inhalation

Dose-dependent increase of FEV1, FVC and FEF50
- formoterol: yes
- salmeterol: no

FEV1:
- formeterol 12ug < salmeterol 50ug , p<0.05
- formeterol 24ug < salmeterol 50ug, p<0.05
- formeterol 36ug > salmeterol 50ug, p: NR

FEV1 area under the curve:
- formeterol 12ug < salmeterol 50ug , p<0.05
- formeterol 24ug < salmeterol 50ug, p<0.05
- formeterol 36ug vs salmeterol 50ug, p>0.05

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1998a — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: Italy

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	16	0 /	0 /	16

Inclusion criteria:

Fulfilled American Thoracic Society critiera for diagnosis of COPD; > 40 years old, current or former smokers (>10 pack-years) w/o hx of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnea when walking quietly o

Exclusion criteria:

Patients with allergic rhinitis, atopy, skin-test positivity or with a total blood eosinophil count >400 cells/mm3 were excluded; any coexisting cardiovascular or lung disorder.

Comments:

Population: **Mean age:** NR years
Gender: NR% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 24ug	24 ug	16	NR	NR
Salmeterol 50ug	50 ug	16	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC

Formoterol 24ug		Salmeterol 50ug	
16	1.81(NR)	16	1.84(NR)
16	2.2(NR)	16	2.15(NR)
	0.39(NR)		0.31(NR)

FEV1

Formoterol 24ug		Salmeterol 50ug	
16	0.99(NR)	16	1.03(NR)
16	1.33(NR)	16	1.3(NR)
	0.34(NR)		0.27(NR)

Formoterol 24ug vs Salmeterol 50ug, p value: 0.29

Other Efficacy/Effectiveness Outcomes and Comments:

Albuterol induced a large dose-dependent increase in FEV1 and FVC. Maximum values of bronchodilation of all the treatments were statistically different ($p<0.05$) from their postinhalational baseline levels. However, statistical analysis showed no significant differences ($p=0.61$) between treatment.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1998a — Quality rating (Efficacy, Safety): Fair, Fair

Adverse Events:

Heart rate, after cumulative doses of albuterol

Formoterol 24ug		Salmeterol 50ug	
16	80.0(NR)	16	77.9(NR)
16	81.3(NR)	16	82.3(NR)
	1.3(NR)		4.4(NR)

Formoterol 24ug vs Salmeterol 50ug, p value: >0.05

Notes: NSD between groups in maximum heart rate

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1998b **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT SB Crossover **Run-in :** no days **Setting:** NR
Country: Italy

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	12	0 /	0 /	12

Inclusion criteria:

Fulfilled criteria of the American Thoracic Society for diagnosis of COPD; > 40 years old, current or former smokers (>10 pack-years) w/o hx of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnea when walking qui

Exclusion criteria:

None of the patients had recent myocardial infarction, decompensated heart failure, unstable angina, or known severe arrhythmias.

Comments:

Population: **Mean age:** 60.2 years
Gender: 25% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	12ug	12	60.2 years	25% Female
Formoterol 24ug	24ug	12	60.2 years	25% Female
Salmeterol 50ug	50ug	12	60.2 years	25% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate, increase

Formoterol 12ug vs Salmeterol 50ug, p value: >0.05

Notes: Heart rate (data NR, only graphs):
- formoterol 24ug > formoterol 12ug (p<0.05)
- formoterol 24ug > salmeterol 50ug (p<0.05)
- formoterol 12ug vs salmeterol 50ug (p<0.05)

Ventricular PBs, mulitform, no. of patients

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	2(17)	12	3(25)	12	0(0)
	NR(NR)		NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Cazzola, 1998b — Quality rating (Efficacy, Safety): Fair, Fair

Ventricular PBs, paired, no. of patients

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	0(0)	12	1(8)	12	0(0)
	NR(NR)		NR(NR)		NR(NR)

Ventricular PBs, several, no. of pts in any hour

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	4(33)	12	4(33)	12	3(25)
	NR(NR)		NR(NR)		NR(NR)

Ventricular PBs, isolated, no. of patients

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	6(58)	12	7(25)	12	5(42)
	NR(NR)		NR(NR)		5(NR)

Ventricular PBs, no. of patients after treatment

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	12(100)	12	12(100)	12	11(92)
	NR(NR)		NR(NR)		NR(NR)

Ventricular PBs, mean

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	2.6(2.9)	12	3.2(4.7)	12	2.2(3.5)
	NR(NR)		NR(NR)		NR(NR)

K+, maximum decrease in plasma level

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug QD	
12	NR(NR)	12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)	12	NR(NR)
	-0.49(NR)		-1.12(NR)		-0.45(NR)

Other Adverse Events and Comments:

Form 24ug significantly reduced plasma K+ for 9 hours compared to placebo, form 12ug & sall 50ug reduced K+ for 2 & 6 hours, respectively. NSD in increase in HR btwn form 12ug & sal 50ug; both > placebo ($p<0.05$)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Celik, 1999 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Turkey

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	0 /	0 /	22

Inclusion criteria:

Patients having 160 ml or at least a 10% increase in the baseline FEV1 15min after 200 ug salbutamol with a postbronchodilator FEV1 below the predicted range were accepted as partially reversible and constituted the final eligible study population; allowe

Exclusion criteria:

Patients using beta blocker (including eye drops) or systemic corticosteroid treatment

Comments:

Population: **Mean age:** 57.3 years

Gender: 9.09% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	12ug	22	57.3 years	9.09% Female
Salmeterol 50ug	12ug	22	57.3 years	9.09% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 12ug		Salmeterol 50ug	
22	1.1(0.2)	22	1.1(0.2)
22	1.3(NR)	22	1.21(NR)
	0.2(NR)		0.11(NR)

FVC, AUC average

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	6.7(2.0)	22	3.7(1.3)
	NR(NR)		NR(NR)

FEV1, AUC average

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	3.5(1.3)	22	3.2(1.2)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Celik, 1999 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1

Formoterol 12ug		Salmeterol 50ug	
22	1.1(0.2)	22	1.1(0.2)
22	1.35(NR)	22	1.32(NR)
	0.25(NR)		0.22(NR)

FEV1, maximum

Formoterol 12ug		Salmeterol 50ug	
22	1.1(0.2)	22	1.1(0.2)
22	1.49(NR)	22	1.5(NR)
	0.39(NR)		0.40(NR)

FEV1 at least 15% increase

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	14(64)	22	12(54)
	NR(NR)		NR(NR)

FEV1

Formoterol 12ug		Salmeterol 50ug	
22	1.1(0.2)	22	1.1(0.2)
22	1.35(NR)	22	1.30(NR)
	0.25(NR)		0.20(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

AUC values of FEV1/FVC, % h
FEF25%. L/s h
FEF50%. L/s h
FEF75%. L/s h
FEF25 75%. L/s h
PEFR, L/s h

FEV1: when compared with those having less than 15% reversibility at 20min, patients exhibiting immediate reversibility were found to have a significantly higher maximal bronchodilator response after formoterol (26 vs 37%, p<0.05) and salmeterol (27 vs 38%, p<0.05) inhalation.

Adverse Events:

Palpitations

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	1(5)	22	0(0)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Celik, 1999 **Quality rating (Efficacy, Safety): Fair, Poor**

Headache

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	0(0)	22	1(5)
	NR(NR)		NR(NR)

Tremor

Formoterol 12ug		Salmeterol 50ug	
22	NR(NR)	22	NR(NR)
22	2(9)	22	1(5)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

For pharmacologically predictable AEs, there was no difference between formoterol & salmeterol.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Condemi, 2001 — Quality rating (Efficacy, Safety): Poor, Fair

Design:

Study design: RCT Open Parallel **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	593 /	528	68 /	14 /	460

Inclusion criteria:

Outpatients between the ages of 18 and 75 years with moderate to moderately severe asthma diagnosed at least 1 year before screening. They must have been receiving low-dose inhaled corticosteroids at 400 ug/d (except fluticasone, 200 ug/d) for at least 1

Exclusion criteria:

Pregnant or nursing women; women of child-bearing potential who were not practicing reliable contraception; respiratory diseases unrelated to asthma or other serious medical conditions; if they had required a dose increase in inhaled corticosteroids to tr

Comments:

No significant differences in demographic and baseline characteristics between treatment groups, except in the proportion of current smokers in the formoterol group 12(4.6%) compared with the salmeterol group 4(1.5%), p=0.039.

Population: **Mean age:** NR years
Gender: NR% Female

Intervention:

Duration: 24 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug BID	24ug	262	NR	NR
Salmeterol 50ug BID	100ug	266	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF

Formoterol 12ug		Salmeterol 50ug	
256	359.8(96.9)	260	355.5(96.4)
256	393.4(99.3)	260	371.7(95.6)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.001

Effectiveness Outcomes:

Use of rescue medication, night time

Formoterol 12ug		Salmeterol 50ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	2.8(NR)		4.2(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.03

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Condemi, 2001 — Quality rating (Efficacy, Safety): Poor, Fair

Use of rescue medication, daytime

Formoterol 12ug		Salmeterol 50ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	5.6(NR)		7.7(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.03

Actuation rescue med /wk within 30min of RX drug

Formoterol 12ug		Salmeterol 50ug	
256	0(0)	260	0(NR)
256	1.4(NR)	260	2.1(NR)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.005

Asthma

Formoterol 12ug		Salmeterol 50ug	
262	NR(NR)	266	NR(NR)
262	53(20.2)	266	49(18.4)
	NR(NR)		NR(NR)

Episode-free days

Formoterol 12ug		Salmeterol 50ug	
256	NR(NR)	260	NR(NR)
256	9.5(9.0)	260	7.8(8.7)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.04

Other Efficacy/Effectiveness Outcomes and Comments:

There were no statistically significant differences between treatments in terms of nighttime or daytime symptom scores

Adverse Events:

Viral infection

Formoterol 12ug		Salmeterol 50ug	
262	NR(NR)	266	NR(NR)
262	50(19.1)	266	52(19.5)
	NR(NR)		NR(NR)

No. with at least 1 adverse events

Formoterol 12ug		Salmeterol 50ug	
262	NR(NR)	266	NR(NR)
262	202(77.1)	266	201(75.6)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Condemi, 2001

Quality rating (Efficacy, Safety): Poor, Fair

Back pain

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 4(1.5)	266 19(7.1)
NR(NR)	NR(NR)

Headache

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 18(6.9)	266 13(4.9)
NR(NR)	NR(NR)

Cough

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 11(4.2)	266 15(5.6)
NR(NR)	NR(NR)

Pharyngitis

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 7(2.7)	266 15(5.6)
NR(NR)	NR(NR)

Rhinitis

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 17(6.5)	266 11(4.1)
NR(NR)	NR(NR)

Bronchitis

Formoterol 12ug	Salmeterol 50ug
262 NR(NR)	266 NR(NR)
262 19(7.3)	266 23(8.6)
NR(NR)	NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Condemi, 2001 — Quality rating (Efficacy, Safety): Poor, Fair

Sinusitis

Formoterol 12ug		Salmeterol 50ug	
262	NR(NR)	266	NR(NR)
262	37(14.1)	266	40(15)
	NR(NR)		NR(NR)

Upper respiratory tract infection

Formoterol 12ug		Salmeterol 50ug	
262	NR(NR)	266	NR(NR)
262	68(26)	266	51(19.2)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Di Marco, 2003 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** no days **Setting:** Community practice
Country: Italy

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	20	NR /	NR /	20

Inclusion criteria:

>35 years of age, current or former smoker (>10 packs-year) and a diagnosis of COPD as defined by the American Thoracic Society (ATS), and FEV1/FVC ration of <70% and a baseline severity of breathlessness of at least grade 1 (short of breath when hurrying

Exclusion criteria:

Unstable respiratory status within the previous 4 weeks, a known history of asthma or chronic respiratory disease other than COPD, any clinically significant concurrent disease, and a change in medication for COPD within the 4 weeks prior to the screening

Comments:

Population: **Mean age:** 65 years
Gender: 30% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	12 ug	20	65 years	30% Female
Salmeterol 50ug	100ug	20	65 years	30% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

Inspiratory capacity

NR NR(NR)
NR NR(NR)
NR(NR)

FEV1

Formoterol 12ug		Salmeterol 50ugX2	
20	NR(NR)	20	NR(NR)
20	NR(NR)	20	NR(NR)
	9.1(NR)		6.2(NR)

Effectiveness Outcomes:

Dyspnea symptoms (VAS 0- 20, (+)=improved

Formoterol 12ug

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Di Marco, 2003	Quality rating (Efficacy, Safety): Fair, NA

Salmeterol 50ug

Formoterol 12ug vs Salmeterol 50ug, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

Patients with basal IC <80% pred increase in FEV1 and IC 30mins after drug inhalation
Patients with basal IC >80% pred increase in FEV1 and IC 30mins after drug inhalation

NR

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Eryonucu, 2005 — Quality rating (Efficacy, Safety): NA, Good

Design:

Study design: RCT NR Parallel **Run-in :** NR **Setting:** NR

Country: Turkey

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 39	NR	/ NR	/ 39

Inclusion criteria:

Patients with newly diagnosed or known cases of bronchial asthma were studies. Asthmatic patients were selected conscutively according to the American Thoracic Socieyt guidelines. None of the patients were receiving oral and inhlaed asthma medicatons (bet

Exclusion criteria:

Patients with diabetes mellitus, renal disorders, or any diseases that might have influenced the automomic function were exluced. Examination or a medical history with cardiovascular disease or medication were excluded.

Comments:

Population: **Mean age:** 35.0 years

Gender: 54.0% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	NR	20	34 years	55% Female
Salmeterol 50ug	NR	19	35 years	52.63% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

- HRVM: mean of the SD of all normal to normal intercals in all 5 min intervals
- RMSSD: root mean square of differences between adjacent normal to normal intervals
- SDANN: SD of mean of all normal to normal intervals in all consecutive 5 min segments of the entire recordings
- SDHRV: SD of all normal to normal intervals in all 5 min intervals
- SDNN: SD of all normal to normal intervals

NR

Other Adverse Events and Comments:

SDNN=SD of all normal-to-normal intervals; RMSSD=Root mean square of differences between adjacent normal-to-normal intervals; SDANN=SD of mean of all normal-to-normal intervals in all consecutive 5min segments of the entire recording; HRVM=Mean of the SD in all 5min intervals; SDHRV=SD in all 5min intervals.

Baseline HRV were NSD between form & sal; there were NSDs in HRV parameters after the form & sal inhalation.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 — Quality rating (Efficacy, Safety): Fair-poor, Poor

Design:

Study design: RCT Open Parallel **Run-in :** 7-10 days days **Setting:** Community practice

Country: UK & Ireland

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	156	33 /	6 /	123

Inclusion criteria:

Aged 6-17 years with a clinical diagnosis of asthma, currently managed with short-acting B-2-agonists and an inhaled corticosteroid, who were still experiencing asthma symptoms such as chest tightness, cough, wheeze or shortness of breath on more than 3 d

Exclusion criteria:

All patients with < 7 days of evaluable effectiveness data. Patients recruited from the Republic of Ireland were excluded from the economic evaluation before analysis began. Principle exclusion criteria: PEF < 50% of prediced, asthma symptoms requiring i

Comments:

Population: **Mean age:** 11.7 years

Gender: 44.83% Female

Intervention:

Duration: 12 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug (9ug deli	24ug	79	11.7 years	36.71% Female
Salmeterol 50ug BID	100ug	76	11.8 years	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, at clinic

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
79 317.5(1110.4)	76 311.5(109.2)
79 346.3(NR)	6 329.6(NR)
28.8(50.5)	18.1(48.6)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.355

Effectiveness Outcomes:

% taking >=75% of doses of study medication

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
79	76
79 90	76 88

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Unscheduled GP visits

Formoterol 12ug (9ug delivered dose) BID	
73	NR(NR)
73	0.05(0.23)
	NR(NR)

Salmeterol 50ug BID	
72	NR(NR)
72	0.01(0.12)
	NR(NR)

Parents unable to attend work or activities

Formoterol 12ug (9ug delivered dose) BID	
79	NR(NR)
79	NR(0.76)
	NR(NR)

Salmeterol 50ug BID	
76	NR(NR)
76	NR(3.52)
	NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.071

patient unable to join activities

Formoterol 12ug (9ug delivered dose) BID	
79	NR(NR)
79	NR(7.5)
	NR(NR)

Salmeterol 50ug BID	
76	NR(NR)
76	NR(12.5)
	NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.178

Change in HRQL: Activity; Pt.-reported

Formoterol 12ug (9ug delivered dose) BID	
NR	NR(NR)
NR	NR(NR)
	1.07(NR)

Salmeterol 50ug BID	
NR	NR(NR)
NR	NR(NR)
	0.72(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Notes: Values based on estimates from graph

Limited activity days because of asthma

Formoterol 12ug (9ug delivered dose) BID	
79	NR(NR)
79	NR(NR)
	-0.92(2.03)

Salmeterol 50ug BID	
76	NR(NR)
76	NR(NR)
	-0.66(1.91)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.622

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Change in HRQL: Symptoms; Pt.-reported

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)
1.03(NR)	0.67(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Notes: Values based on estimates from graph

Change in HRQL: Emotion; Pt.-reported

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)
0.86(NR)	0.55(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Notes: Values based on estimates from graph

Change in HRQL: Overall; Parent-reported

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)
0.52(NR)	0.37(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Notes: Values based on estimates from graph

Change in HRQL: Activity; Parent-reported

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug
NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)
0.52(NR)	0.21(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: <0.05

Notes: Values based on estimates from graph

Change in HRQL: Emotion; Parent-reported

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
NR NR(NR)	NR NR(NR)
NR NR(NR)	NR NR(NR)
0.53(NR)	0.42(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Notes: Values based on estimates from graph

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Change in HRQL: Overall; Pt.-reported

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	0.92(NR)		0.54(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: >0.05

Notes: Values based on estimates from graph

Change in PRN B2 agonist use

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	NR(NR)	76	NR(NR)
	-2.45(2.29)		-2.05(2.50)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.043

Notes: Had adjusted for differences in run-in values.

Days study medication usage

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
73	NR(NR)	72	NR(NR)
73	76(19)	72	80(15)
	NR(NR)		NR(NR)

Relevant concomitant meds, days used

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
73	NR(NR)	72	NR(NR)
73	75(24)	72	83(29)
	NR(NR)		NR(NR)

Able to stop using SABA at week 12

Formoterol 12ug (9ug delivered dose) BID	Salmeterol 50ug BID
79	76
79	76

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.04

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Short-acting B2-agonist usage, inhalations

Formoterol 12ug (9ug delivered dose) BID	
73	NR(NR)
73	109(145)
	NR(NR)

Salmeterol 50ug BID	
72	NR(NR)
72	164(178)
	NR(NR)

Change in PRN B2 agonist use, daytime

Formoterol 12ug (9ug delivered dose) BID	
79	NR(NR)
79	NR(NR)
	-1.85(1.90)

Salmeterol 50ug BID	
76	NR(NR)
76	NR(NR)
	-1.72(2.02)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.081

Notes: Had adjusted for differences in run-in values.

Change in PRN B2 agonist use, nighttime

Formoterol 12ug (9ug delivered dose) BID	
76	NR(NR)
76	NR(NR)
	-0.56(0.83)

Salmeterol 50ug BID	
76	NR(NR)
76	NR(NR)
	-0.39(0.69)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.251

Notes: Had adjusted for differences in run-in values.

Use of severe exacerbation meds (eg steroids)

Formoterol 12ug (9ug delivered dose) BID	
73	NR(NR)
73	0.03(0.16)
	NR(NR)

Salmeterol 50ug BID	
72	NR(NR)
72	0(0)
	NR(NR)

Poorly controlled days

Formoterol 12ug (9ug delivered dose) BID	
79	NR(NR)
79	12.4(NR)
	NR(NR)

Salmeterol 50ug BID	
76	NR(NR)
76	17.0(NR)
	NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.107

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Asthma, mild exacerbations

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	79	NR(NR)
79	7.8(NR)	79	12.2(NR)
	NR(NR)		NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Formoterol 12ug BID, p value: 0.051

Severe asthma exacerbation of asthma

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
80	(17)	76	(17)
	NR(NR)		NR(NR)

Clinician asthma severity score (0-3), night

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	NR(NR)	76	NR(NR)
	-0.75(0.94)		-0.51(0.85)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.049

Patient asthma severity score (0-3), night

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	NR(NR)	76	NR(NR)
	-0.5(0.59)		-0.47(0.62)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.687

Patient asthma severity score (0-3), day

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	NR(NR)	76	NR(NR)
	-7.0(0.62)		-0.53(0.57)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.052

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004 **Quality rating (Efficacy, Safety): Fair-poor, Poor**

Clinician asthma severity score (0-3), day

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	NR(NR)	76	NR(NR)
	-0.74(0.88)		-0.61(0.82)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.324

Time to achieve asthma control

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	12(NR)	76	26(NR)
	NR(NR)		NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: 0.175

Other Efficacy/Effectiveness Outcomes and Comments:

As needed beta agonist use by age subgroups
Night time awakenings because of asthma
Patient overall feeling about asthma symptom (0-2)

NR

Adverse Events:

Adverse events reported

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
80	44(55)	76	45(59)
	NR(NR)		NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: >0.05

Headache

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
80	14(17.5)	76	17(22.4)
	NR(NR)		NR(NR)

Drug discontinuation due to asthma deterioration

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
79	5(6.4)	76	4(3.3)
	NR(NR)		NR(NR)

Formoterol 12ug (9ug delivered dose) BID vs Salmeterol 50ug BID, p value: NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Everden, 2002; Everden, 2004	Quality rating (Efficacy, Safety): Fair-poor, Poor

Upper respiratory tract infection

Formoterol 12ug (9ug delivered dose) BID		Salmeterol 50ug BID	
79	NR(NR)	76	NR(NR)
80	7(8.8)	76	9(11.8)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Grembiale, 2005 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: Italy

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	10	0 /	0 /	10

Inclusion criteria:

Patients with mild, moderate or severe asthma. All subjects were positive to prick-skin-test and had a clinical history of episodic or recurrent dyspnoea and wheezing. Moreover, they had previously exhibited an increase in FEV1 of at least 15% with respec

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 53.2 years
Gender: 30% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	NR	10	53.2 years	30% Female
Salmeterol 50ug	NR	10	53.2 years	30% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 12ug		Salmeterol 50ug	
10	2.03(0.82)	10	2.04(0.82)
10	2.37(0.87)	10	2.37(0.93)
	NR(NR)		NR(NR)

FEV1

Formoterol 12ug		Salmeterol 50ug	
10	2.03(0.82)	10	2.04(0.82)
10	2.45(0.91)	10	2.3(0.85)
	NR(NR)		NR(NR)

FEV1

Formoterol 12ug		Salmeterol 50ug	
10	2.03(0.8)	10	2.04(0.84)
10	2.22(0.83)	10	2.05(0.83)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Grembiale, 2005	Quality rating (Efficacy, Safety): Fair, Poor

FEV1, maximum

Formoterol 12ug		Salmeterol 50ug	
10	2.03(0.8)	10	2.04(0.84)
10	2.63(0.98)	10	2.55(0.98)
	NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: <0.05

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

No side effect was observed during this short trial.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Grove, 1996 — Quality rating (Efficacy, Safety): Poor, Good

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** NR
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 10	NR	/ NR	/ 10

Inclusion criteria:

All patients were diagnosed as having asthma according to the American Thoracic Society criteria. At an initial screening visit patients were required to have an FEV1 of less than 80% of predicted normal, and to demonstrate at least 15% reversibility to i

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 37 years
Gender: 50% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	NR	10	37 years	50% Female
Salmeterol 25ug	NR	10	37 years	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR

Formoterol 12ug		Salmeterol 25ug	
10	338(34.79)	10	358(34.79)
10	415(34.79)	10	408(34.79)
	NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 25ug, p value: >0.05

FEV25 75

Formoterol 12ug		Salmeterol 25ug	
10	1.40(0.44)	10	1.37(0.44)
10	1.83(0.41)	10	1.96(0.41)
	NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 25ug, p value: >0.05

FEV1

Formoterol 12ug		Salmeterol 25ug	
10	2.1(0.28)	10	2.14(0.28)
10	2.5(0.22)	10	2.41(0.22)
	NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 25ug, p value: >0.05

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Grove, 1996 — Quality rating (Efficacy, Safety): Poor, Good

Other Efficacy/Effectiveness Outcomes and Comments:

dose response curves to fenoterol

There were no results comparing formoterol and salmeterol, but only to placebo.

Adverse Events:

Heart rate

Formoterol 12ug		Salmeterol 25ug	
10	76(6.32)	10	71(6.32)
10	72(6.32)	10	70(6.32)
	NR(NR)		NR(NR)

K+

Formoterol 12ug		Salmeterol 25ug	
10	4.02(0.19)	10	3.86(0.16)
10	3.97(0.19)	10	3.93(0.19)
	NR(NR)		NR(NR)

Tremor

Formoterol 12ug		Salmeterol 25ug	
10	2.25(0.51)	10	2.31(0.47)
10	2.27(0.32)	10	2.09(0.28)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Kottakis, 2002 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** No days **Setting:** NR

Country: Multinational

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	68 /	50 /	47	2 /	0 /	47

Inclusion criteria:

Male and female patients with stage II and III COPD diagnosed according to the American Thoracic Society criteria; age 40 years or older; current or previous smoker (more than 20 packs-year); prebronchodilator baseline FEV1 < 50% of predicted normal valu

Exclusion criteria:

Current or childhood asthma; a history of allergic rhinitis or another atopic disease; a total blood eosinophil count higher tha 400/uL; a respiratory tract infection within one month before screening; hospitalization or emergency room treatment for an ac

Comments:

All patients who were included achieved the minimum value of 5% reversibility, and only one patient failed to meet the inclusion criterion maximum limit for reversibility (12%), with an increase of 13% of predicted normal. This patient was not excluded fr

Population: **Mean age:** 63.5 years

Gender: 19.15% Female

Intervention:

Duration: Single dose for 5 days NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	Single dose	47	8.6 years	19.15% Female
Formoterol 24ug	Single dose	47	8.6 years	19.15% Female
Salmeterol 50ug	Single dose	47	8.6 years	19.15% Female
Salmeterol 100ug	Single dose	47	8.6 years	19.15% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)
47	1.50(NR)	47	1.54(NR)	47	1.41(NR)	47	1.41(NR)
	0.33(NR)		0.37(NR)		0.24(NR)		0.24(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0349

FVC

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0012

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Kottakis, 2002 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)
47	1.51(NR)	47	1.47(NR)	47	1.37(NR)	47	1.37(NR)
	0.34(NR)		0.3(NR)		0.2(NR)		0.2(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0123

FEV1

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	1.17(0.27)	47	1.17(0.27)	47	1.17(0.27)	47	1.17(0.27)
47	1.49(NR)	47	1.52(NR)	47	1.39(NR)	47	1.40(NR)
	0.32(NR)		0.35(NR)		0.22(NR)		0.23(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0105

FEV1

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)
47	1.46(NR)	47	1.54(NR)	47	1.42(NR)	47	1.43(NR)
	0.29(NR)		0.37(NR)		0.25(NR)		0.26(NR)

FVC

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0001

FVC, AUC 0-1h

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0135

FEV1, maximum

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)	47	1.17(0.29)
47	1.58(NR)	47	1.63(NR)	47	1.54(NR)	47	1.46(NR)
	0.41(NR)		0.46(NR)		0.37(NR)		0.29(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0948

Formoterol 24ug vs Salmeterol 50ug, p value: 0.0004

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Kottakis, 2002 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1 at least 15% increase, no. of pts

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	NR(NR)	47	NR(NR)	47	NR(NR)	47	NR(NR)
47	23(49)	47	32(68)	47	7(15)	47	9(19)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1, AUC 0-1hr

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
NR	NR(NR)	47	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	47	NR(NR)	NR	NR(NR)	NR	NR(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0044

Formoterol 24ug vs Salmeterol 100ug, p value: 0.0001

Effectiveness Outcomes:

Effort to breathe (VAS)

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	NR(NR)	47	NR(NR)	47	NR(NR)	47	NR(NR)
44	NR(NR)	45	NR(NR)	45	NR(NR)	46	NR(NR)
	-1.4(1.3)		-1.4(1.4)		-1.1(1.3)		-1.0(1.3)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0853

Notes: Between group mean difference was the end point difference.

Degree of breathing discomfort (VAS)

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.0646

Degree of breathing discomfort (VAS)

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.1519

Effort to breathe (VAS)

Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug		Salmeterol 100ug	
47	NR(NR)	47	NR(NR)	47	NR(NR)	47	NR(NR)
44	NR(NR)	45	NR(NR)	45	NR(NR)	46	NR(NR)
	-0.8(1.2)		-0.8(1.4)		-0.6(1.0)		-0.8(1.4)

Formoterol 12ug vs Salmeterol 50ug, p value: 0.1984

Notes: Between group mean difference was the end point difference.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Kottakis, 2002 **Quality rating (Efficacy, Safety): Fair, Poor**

Other Efficacy/Effectiveness Outcomes and Comments:

Time(min) to 10%, 12%, 15% maximum change from baseline FEV1
IC AUC 0-1h
FEF 25-75% AUC 0-1h

FEV1 data NR, shown only in graphs

Other Adverse Events and Comments:

Two pts had AEs that led to discontinuation; both pts experienced a COPD exacerbation of moderate severity that was judged to be unrelated to the study drug; there were no differences in BP or PR.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Nightingale, 2002 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT Open Crossover **Run-in :** 14 days days **Setting:** Community practice
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 42	15	/ 0	/ 38

Inclusion criteria:

Nonsmoking patients who met the American Thoracic Society criteria for asthma; All patients were receiving treatment with dosages of at least 1500ug of an inhaled steroid or of regular oral steroids and had and FEV1 < 80% predicted, reported daily asthma

Exclusion criteria:

Patients who had taken LABA for four weeks prior to the study.

Comments:

Investigators were blinded throughout the trial. Patients were only partially blinded. They were unaware of whether they were receiving formoterol or placebo but were aware of treatment with salmeterol because the inhaled differed in appearance.

Population: **Mean age:** 45.4 years
Gender: 69.05% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug BID	24ug	42	45.4 years	69.05% Female
Salmeterol 50ug BID	100ug	42	45.4 years	69.05% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, mean

Formoterol 12ug		Salmeterol 50ug	
42	333(90.73)	42	333(90.73)
35	357(100.57)	33	363(91.91)
	NR(NR)		NR(NR)

FEV1

Formoterol 12ug		Salmeterol 50ug	
42	1.83(0.78)	42	1.83(0.78)
35	1.96(0.83)	33	1.91(0.75)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Nightingale, 2002 — Quality rating (Efficacy, Safety): Fair, Poor

PEF, morning

Formoterol 12ug		Salmeterol 50ug	
42	290(82.83)	42	290(90.73)
35	304.4(NR)	33	304.8(NR)
	14.4(NR)		14.8(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: >0.05

Effectiveness Outcomes:

No. of rescue inhaler use

Formoterol 12ug		Salmeterol 50ug	
42	6.1(4.54)	42	6.1(4.54)
35	4.1(5.32)	35	3.6(4.73)
	NR(NR)		NR(NR)

Nighttime symptom score

Formoterol 12ug		Salmeterol 50ug	
42	0.9(0.65)	42	0.9(0.65)
35	0.6(0.59)	33	0.4(0.57)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: 0.20

Daytime symptom score

Formoterol 12ug		Salmeterol 50ug	
42	1.2(0.65)	42	1.2(0.65)
35	0.9(0.59)	33	0.8(0.57)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: 0.05

Other Efficacy/Effectiveness Outcomes and Comments:

There were no significant treatment effects.

Adverse Events:

Total adverse events

Formoterol 12ug		Salmeterol 50ug	
42	NR(NR)	42	NR(NR)
35	17(48.6)	33	13(39.4)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

Serious AE: one patient experienced a transient ischemic attach while taking formoterol.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Palmqvist, 1997 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Sweden

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 28	NR	/ NR	/ 28

Inclusion criteria:

Only nonsmoking stable asthmatic patients (18-70 years of age) with FEV1 >40% predicted were included. A reversibiliy of at least 10% of FEV1 should be seen 30 min after 100ug salbutamol delivered by pMDI. An additional increase of FEV1 after a total dose

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 45.6 years

Gender: 60.71% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 6ug	NR	28	45.6 years	60.71% Female
Formoterol 12ug	NR	28	45.6 years	60.71% Female
Formoterol 24ug	NR	28	45.6 years	60.71% Female
Salmeterol 50ug	NR	28	45.6 years	60.71% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1 at least 15% increase, no. of pts

Formoterol 6ug		Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	12(43)	28	19(68)	28	18(64)	28	17(61)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1

Formoterol 6ug		Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug	
28	2.32(NR)	28	2.32(NR)	28	2.26(NR)	28	2.31(NR)
28	2.62(0.68)	28	2.68(0.68)	28	2.71(0.70)	28	2.65(0.62)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Palmqvist, 1997 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, duration of effect, at least 15% increased

Formoterol 6ug		Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	244(NR)	28	337(NR)	28	459(NR)	28	345(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Medication onset time

Formoterol 6ug		Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	NR(NR)	28	12.4(NR)	28	3.6(NR)	28	31.0(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Formoterol 12ug vs Salmeterol 50ug, p value: <0.05

Formoterol 24ug vs Salmeterol 50ug, p value: <0.05

Other Efficacy/Effectiveness Outcomes and Comments:

FEV1:
- 3min: formoterol 6ug > salmeterol 50ug, p<0.05
- 15min: formoterol 6ug vs salmeterol 50ug, p>0.05
- 12hr: formoterol 6ug < formoterol 24ug, p<0.05
- 12hr: formoterol 12ug < formoterol 24ug, p<0.05
- 12hr: formoterol 24ug vs salmeterol 50ug, p>0.05

Dose comparison, mean 12h average:
- formoterol 9ug = salmeterol 50ug
- formoterol 6ug vs salmeterol 50ug, p>0.05
- formoterol 12ug vs salmeterol 50ug, p>0.05
- formoterol 24ug > salmeterol 50ug, p<0.05

Adverse Events:

Tachycardia, palpitation and tremor

Formoterol 6ug		Formoterol 12ug		Formoterol 24ug		Salmeterol 50ug	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	1(4)	28	1(4)	28	5(18)	28	0(0)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

Headache was observed in 6 to 7 pts after all treatments.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Pohunek, 2004 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** no days **Setting:** NR
Country: Czech

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	71	4 /	2 /	64

Inclusion criteria:

Children (7-12) and adolescents (13-17) who had moderate-to-severe asthma according to the GINA definition for more than six months were enrolled into the study. Patients were recruited from nine outpatient clinics throughout the Czech Republic. To be inc

Exclusion criteria:

Patients could not be enrolled if they showed any signs of clinically relevent concomitant disease, were taking oral corticosteroids or beta-blockers, or had a significant seasonal allergy or a recent respiratory infection.

Comments:

Population: **Mean age:** 11.9 years
Gender: NR% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 4.5ug (=6 ug d	single dose	68	11.9 years	NR
Formoterol 9ug (=12 ug d	single dose	68	11.9 years	NR
Formoterol 18ug (=24ug d	single dose	68	11.9 years	NR
Formoterol 36ug (=48 ug	single dose	68	11.9 years	NR
Salmeterol 50ug	single dose	68	11.9 years	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)
43	2.11(NR)	41	2.19(NR)	44	2.25(NR)	44	2.30(NR)	42	2.05(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Formoterol 4.5ug vs Salmeterol 50ug, p value: NS

Formoterol 9ug vs Salmeterol 50ug, p value: <0.05

Formoterol 18ug vs Salmeterol 50ug, p value: <0.05

Formoterol 36ug vs Salmeterol 50ug, p value: <0.05

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Pohunek, 2004 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1, maximum

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)
43	2.35(NR)	41	2.40(NR)	44	2.45(NR)	44	2.49(NR)	42	2.30(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Formoterol 4.5ug vs Salmeterol 50ug, p value: NS

Formoterol 9ug vs Salmeterol 50ug, p value: <0.05

Formoterol 18ug vs Salmeterol 50ug, p value: <0.05

Formoterol 36ug vs Salmeterol 50ug, p value: <0.05

FEV1, average 12h serial

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)	68	1.97(NR)
43	2.17(NR)	41	2.25(NR)	44	2.29(NR)	44	2.33(NR)	42	2.14(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Formoterol 4.5ug vs Salmeterol 50ug, p value: NS

Formoterol 9ug vs Salmeterol 50ug, p value: <0.05

Formoterol 18ug vs Salmeterol 50ug, p value: <0.05

Formoterol 36ug vs Salmeterol 50ug, p value: <0.05

Other Efficacy/Effectiveness Outcomes and Comments:

Clear dose dependent effects
Therapeutic ratio

Onset of effect (> indicates faster onset):
- formoterol 4.5ug vs salmeterol 50ug, NS
- formoterol 9ug > salmeterol 50ug, p=0.0007
- formoterol 18ug > salmeterol 50ug, p=0.0093
- formoterol 36ug > salmeterol 50ug, p=0.0002

Adverse Events:

Palpitations

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)
68	0(0)	68	0(0)	68	0(0)	68	0(0)	68	0(0)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Headache

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)
68	0(0)	68	0(0)	68	0(0)	68	0(0)	68	0(0)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Pohunek, 2004 **Quality rating (Efficacy, Safety): Fair, Poor**

Tremor

Formoterol 4.5ug		Formoterol 9ug		Formoterol 18ug		Formoterol 36ug		Salmeterol 50ug	
68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)	68	NR(NR)
68	0(0)	68	0(0)	68	0(0)	68	1(1.5)	68	0(0)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

The reported AEs were generally of mild or moderate intensity; most common AEs were respiratory disorders (rhinitis & respiratory infection); there are no different between the treatments.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Richter, 2002 **Quality rating (Efficacy, Safety): Fair, NA**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice

Country: Germany

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	25	0 /	0 /	25

Inclusion criteria:

All patients had mild to moderate asthma according to international guideline, FEV1 >= 60% pred, a history of exercise-induced bronchoconstriction and documented hyperresponsiveness to inhaled methacholine (provocative concentration causing a 20% fall in

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 33 years

Gender: 40% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug	NR	25	33 years	40% Female
Salmeterol 50ug	NR	25	33 years	40% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, 60min interval between treatment & exercise

Formoterol 12ug		Salmeterol 50ug	
25	4.14(0.9)	25	3.88(0.85)
25	3.897(NR)	25	3.604(NR)
	-0.243(0.34)		-0.276(0.38)

FEV1, 30min interval between treatment & exercise

Formoterol 12ug		Salmeterol 50ug	
25	4.07(0.9)	25	3.93(0.9)
25	3.837(NR)	25	3.634(NR)
	-0.233(0.26)		-0.296(0.34)

FEV1, 5min interval between treatment & exercise

Formoterol 12ug		Salmeterol 50ug	
25	3.90(0.85)	25	3.68(0.85)
25	3.811(NR)	25	3.438(NR)
	-0.089(0.27)		-0.242(0.42)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Richter, 2002 **Quality rating (Efficacy, Safety): Fair, NA**

Other Efficacy/Effectiveness Outcomes and Comments:

Efficacy outcomes were compared to the pre-exercise value after the treatments.
No significant difference between formoterol and salmeterol for any of the interval.

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Schermer, 2004 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** 14-28 days day **Setting:** Community practice
Country: Netherlands

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ 37	/ 35	3	/ 1	/ 34

Inclusion criteria:

Had to exhibit the clinical asthma features as described by the American Thoracic Society; >= 18 years and had been clinically stable >= 4 weeks before randomization (i.e. no change in regular asthma therapy, no exacerbations or respiratory infections). P

Exclusion criteria:

Treatment with LABA < 14 days prior to the first treatment period; hypersensitive for study medication; cardiac disease or congestive heart failure; electrocardograhic abnormalities; diastolic blood pressure > 100 mmHg; thyroid dysfunction; insulin-treate

Comments:

Population: **Mean age:** 52.7 years
Gender: 57.14% Female

Intervention:

Duration: 12-17 day

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug BID	24ug	35	52.7 years	57.14% Female
Salmeterol 50ug BID	100ug	35	52.7 years	57.14% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, Pre-brochodilator

Formoterol 12ug		Salmeterol 50ug	
34	NR(NR)	34	NR(NR)
34	NR(NR)	32	NR(NR)
	2.29(NR)		2.29(NR)

No. of patient onset-of-action 6' after inhalation

Formoterol 12ug		Salmeterol 50ug	
34	NR(NR)	34	NR(NR)
32	14(27)	32	9(64)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Formoterol 12ug BID, p value: 0.063

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Schermer, 2004 — Quality rating (Efficacy, Safety): Fair, NA

No. of patient onset-of-action 3' after inhalation

Formoterol 12ug		Salmeterol 50ug	
34	NR(NR)	34	NR(NR)
32	12(36)	32	4(13)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: 0.008

FEV1, end treatment

Formoterol 12ug		Salmeterol 50ug	
34	NR(NR)	34	NR(NR)
34	NR(NR)	32	NR(NR)
	0.27(1.05)		0.28(0.91)

FEV1, start treatment

Formoterol 12ug		Salmeterol 50ug	
34	NR(NR)	34	NR(NR)
34	NR(NR)	32	NR(NR)
	0.45(1.05)		0.46(1.02)

Effectiveness Outcomes:

Treatment preference

Formoterol 12ug		Salmeterol 50ug		No preference	
34	NR(NR)	34	NR(NR)	34	NR(NR)
32	17(50)	32	10(29)	32	6(18)
	NR(NR)		NR(NR)		NR(NR)

Notes: The distribution of subjects over these preference categories was statistically significant, p<0.001

Other Efficacy/Effectiveness Outcomes and Comments:

Perception of bronchodilation

NR

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

van Noord, 1996 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice

Country: Netherlands

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	30	0 /	0 /	30

Inclusion criteria:

Adults with asthma who met the American Thoracic Society (ATS) diagnosis criteria for asthma and volunteered to participate in the study. To be included in the study they had to fulfill the following criteria: age 18-70 years; in a stable phase of asthma,

Exclusion criteria:

Any concomintant disorders such as liver, kidney or metabolic disease, and had not history of pulmonary infection or acute exacerbation of their asthma during the previous 6 weeks. The use of beta-blockers or any experimental drug in the four weeks prior

Comments:

Population: **Mean age:** 54 years

Gender: 26.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 24ug	NR	30	54 years	26.67% Female
Salmeterol 50ug	NR	30	54 years	26.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Formoterol 24ug		Salmeterol 50ug	
30	1.88(0.6)	30	1.88(0.6)
30	2.07(NR)	30	2.09(NR)
	0.19(NR)		0.21(NR)

FEV1, maximum

Formoterol 24ug		Salmeterol 50ug	
30	1.88(0.6)	30	1.88(0.6)
30	2.39(NR)	30	2.35(NR)
	0.51(NR)		0.47(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Specific airway conductance (sGaw)

Area under the curve (AUC):
- formoterol vs salmeterol, p>0.05

Onset of action:
- first hour and 30 mins: formoterol vs salmeterol, p>0.05

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

van Noord, 1996 **Quality rating (Efficacy, Safety): Fair, Poor**

- afterward: formoterol (greater improvement than) salmeterol, p value NR

Other Adverse Events and Comments:

There were no AEs reported & the safety screen showed no abnormal data.
There were no significant changes in systolic & diastolic BP except for a drop in the diastolic BP on the formoterol day at the 4h time point. This phenomenon was witnessed previously directly after the consumption of a warm meal.
HR did not change significantly during the three test days.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Verini, 1998 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT NR Crossover **Run-in :** NR **Setting:** NR

Country: Italy

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	27	NR /	NR /	27

Inclusion criteria:

Mild/moderate persistent asthma (level 2 or 3 accoring to WHO assessment) and were skin positive for one or more of the most common allergens in our country: mites (Dermatophagoides), moulds (Alternaria, Aspergillus, Cladosporium), pollens (grass, paretia

Exclusion criteria:

Recent exposure to the relevant allergens in the last 30 days; airway infrection within 4 weeks of the challenges; recent administration (within 2 weeks) of oral long-acting beta-2-agonists, theophylline, sodium cromoglycate, antihistamines or corticoster

Comments:

Population: **Mean age:** 9.1 years

Gender: 33.33% Female

Intervention:

Duration: Single dose, 5 days

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 24ug	ıgle dose for 5 da	27	9.1 years	33.33% Female
Salmeterol 50ug	ıgle dose for 5 da	27	9.1 years	33.33% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF

Formoterol 24ug		Salmeterol 50ug	
27	101.42(NR)	27	103.96(NR)
27	NR(NR)	27	NR(NR)
	14.53(16.46)		8.65(8.29)

FVC

Formoterol 24ug		Salmeterol 50ug	
27	100.08(NR)	27	100.41(NR)
27	NR(NR)	27	NR(NR)
	3.28(7.84)		2.51(9.41)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Verini, 1998	Quality rating (Efficacy, Safety): Fair, NA

FEV1

Formoterol 24ug		Salmeterol 50ug	
27	98.31(NR)	27	99.41(NR)
27	NR(NR)	27	NR(NR)
	8.36(12.36)		7.62(7.66)

PEF

Formoterol 24ug		Salmeterol 50ug	
27	101.42(NR)	27	103.96(NR)
27	NR(NR)	27	NR(NR)
	11.52(10.86)		5.58(8.60)

FVC

Formoterol 24ug		Salmeterol 50ug	
27	100.08(NR)	27	100.41(NR)
27	NR(NR)	27	NR(NR)
	2.67(6.71)		1.72(9.70)

FEV1

Formoterol 24ug		Salmeterol 50ug	
27	98.31(NR)	27	99.41(NR)
27	NR(NR)	27	NR(NR)
	7.71(9.61)		4.89(7.58)

Other Efficacy/Effectiveness Outcomes and Comments:

Mean maximal expiratory flow
Vmax50, maximal expiratory flow at 50% of FVC
Vmax25

NR

Other Adverse Events and Comments:

NR

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT Open Parallel **Run-in :** 2 weeks days **Setting:** Community practice

Country: Multinational

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	529 /	482	54 /	1 /	425

Inclusion criteria:

Patients 18 years of age and older with asthma diagnosed for more than 1 year before study entry who, according to their respiratory physcian, could benefit from the regular use of LABA; required to have used inhaled corticosteroids at a constant dose >=

Exclusion criteria:

Other respiratory diseases, cardiovascular diseases, uncontrolled hypertensiton (diastolic blood pressure > 100mmHg), hyperthroidism, diabetes mellitus, neuromuscular disease, pregnant women, nursing mothers or women not practising a reliable form of cont

Comments:

Population: **Mean age:** 48 years

Gender: 54.15% Female

Intervention:

Duration: 24 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Formoterol 12ug BID	24ug	241	48 years	55.19% Female
Salmeterol 50ug BID	50ug	241	47 years	53.11% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, mean evening pre-dose, month 4

NR NR(NR)
NR NR(NR)
NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.05

PEF, mean evening pre-dose, month 3

NR NR(NR)
NR NR(NR)
NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.05

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998 **Quality rating (Efficacy, Safety): Fair, Fair**

PEF, mean evening pre-dose, month 2

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: <0.05

PEF, mean morning pre-dose, the last 7 days

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: NR

Effectiveness Outcomes:

Inpatients hospital days per patient

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	0.58(5.38)	241	0.43(3.5)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 25ug BID, p value: 0.996

Health professional contacts per patient

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	0.49(1.33)	241	0.59(1.91)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 25ug BID, p value: 0.597

ER visits per patient

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	0.027(0.2)	241	0.095(0.78)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 25ug BID, p value: 0.188

Days unable to perform usual activities

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	4.09(24.32)	241	6.3(21.59)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: 0.439

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998 **Quality rating (Efficacy, Safety): Fair, Fair**

Days of absence from paid work/patient

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	3.19(16.0)	241	2.60(16.1)
	NR(NR)		NR(NR)

Formoterol 12ug BID vs Salmeterol 50ug BID, p value: 0.144

% of patients with QOL improved

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	154(64)	241	149(62)
	NR(NR)		NR(NR)

Notes: Quality of Life was measured using St. George Respiratory Questionnaire

No. of rescue medication, nighttime

Formoterol 12ug		Salmeterol 50ug	
241	1.2(NR)	241	1.1(NR)
NR	0.6(NR)	NR	0.5(NR)
	NR(NR)		NR(NR)

Notes: No data reported.Values estimated from graph.

No. of rescue medication, daytime

Formoterol 12ug		Salmeterol 50ug	
241	2.2(NR)	241	1.9(NR)
NR	0.9(NR)	NR	0.9(NR)
	NR(NR)		NR(NR)

Notes: No data reported.Values estimated from graph.

No. of rescue medication, nighttime

Formoterol 12ug		Salmeterol 50ug	
241	1.2(NR)	241	1.1(NR)
NR	0.35(NR)	NR	0.45(NR)
	NR(NR)		NR(NR)

Notes: No data reported.Values estimated from graph.

No. of rescue medication, daytime

Formoterol 12ug		Salmeterol 50ug	
241	2.2(NR)	241	1.9(NR)
NR	0.5(NR)	NR	0.65(NR)
	NR(NR)		NR(NR)

Notes: No data reported.Values estimated from graph.

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998 **Quality rating (Efficacy, Safety): Fair, Fair**

Respiratory symptom score at nighttime

Formoterol 12ug		Salmeterol 50ug	
241	0.6(NR)	241	0.5(NR)
NR	0.3(NR)	NR	0.3(NR)
	NR(NR)		NR(NR)

Respiratory symptom score at daytime

Formoterol 12ug		Salmeterol 50ug	
241	0.9(NR)	241	0.8(NR)
NR	0.6(NR)	NR	0.5(NR)
	NR(NR)		NR(NR)

Episode free days

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	97(64)	241	95(62)
	NR(NR)		NR(NR)

Respiratory symptom score at daytime

Formoterol 12ug		Salmeterol 50ug	
241	0.6(NR)	241	0.5(NR)
NR	0.4(NR)	NR	0.4(NR)
	NR(NR)		NR(NR)

Asthma, exacerbation

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	4(1.7)	241	4(1.7)
	NR(NR)		NR(NR)

Asthma, excerbations

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	41(17)	241	54(22)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998 **Quality rating (Efficacy, Safety): Fair, Fair**

Respiratory symptom score at nighttime, month 6

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Adverse events assessed by the investigator

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	32(13)	241	21(9)
	NR(NR)		NR(NR)

Overall adverse events

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	190(79)	241	193(80)
	NR(NR)		NR(NR)

Palpitations

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	4(1.7)	241	0(0)
	NR(NR)		NR(NR)

Headache

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	7(2.9)	241	11(4.6)
	NR(NR)		NR(NR)

Tremor

Formoterol 12ug		Salmeterol 50ug	
241	NR(NR)	241	NR(NR)
241	5(2)	241	2(0.8)
	NR(NR)		NR(NR)

Evidence Table 3. Formoterol vs salmeterol - RCTs: efficacy and safety

Vervloet, 1998; Rutten-van Molken, 1998	Quality rating (Efficacy, Safety): Fair, Fair

Other Adverse Events and Comments:

NR

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Carl, 2003 — Quality rating (Efficacy, Safety): Good, Fair

Design:

Study design: RCT DB Parallel **Run-in :** NA **Setting:** ED and inpatient unit
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 552	NA	/ 5	/ 547

Inclusion criteria:

All children between 1 and 18 years of age with physician-diagnosed asthma presenting to the Pediatric Emergency Department of Rainbow Babies and Children's Hospital in Cleveland Ohio, between April 2000 and December 2000 for treatment of acute asthma

Exclusion criteria:

Experiencing a first episode of wheezing, were not currently being treated for asthma, were pregnant, had known hypersensitivity to albuterol, or had cystic fibrosis, cyanotic or uncorrected congenital heart disease, chronic neonatal lung disease, or othe

Comments:

Population: **Mean age:** 7.1 years
Gender: 33% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg	0min, max 6 dos	269	7.2 years	32.71% Female
Levalbuterol 1.25mg	0min, max 6 dos	278	7.1 years	33.09% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

SaO2 at admission

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	95.5(2.5)	278	94.2(6.0)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.26

Effectiveness Outcomes:

Hospital admissions

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	122(45.4)	278	101(36.3)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.02

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Carl, 2003 — Quality rating (Efficacy, Safety): Good, Fair

Length of stay in ER

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	2.2(0.8)	278	2.3(0.9)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.25

NNT with levalbuterol to prevent 1 admission

Albuterol 2.5mg		Levalbuterol 1.25mg	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: <0.05

Risk of admission, with >3 aerosols 12hrs prior

Albuterol 2.5mg		Levalbuterol 1.25mg	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.04

Respiratory rate

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	35.6(12.6)	278	37.0(10.4)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.26

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	129.7(25.5)	278	130.1(23.3)
	NR(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: 0.94

Nausea and vomitting

Albuterol 2.5mg		Levalbuterol 1.25mg	
269	NR(NR)	278	NR(NR)
269	1(0.37)	278	1(0.35)
	NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Carl, 2003	Quality rating (Efficacy, Safety): Good, Fair

Other Adverse Events and Comments:

NR

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Cockcroft, 1997 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** None **Setting:** Research Center
Country: Canada

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	12	0	0	12

Inclusion criteria:
Volunteers with well-controlled asthma; could remain off inhaled B2 agonists during the study and for 4 weeks prior. Fev1>=70% of expected. No exposure to allergens or respiratory tract infections for >=4 weeks prior.

Exclusion criteria:
None reported.

Comments:

Population: **Mean age:** 23.58 years
Gender: 50% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg	2.5 mg	12	23.58 year	50% Female
Levalbuterol 1.25mg	1.25 mg	12	23.58 year	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, % change

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	12.4(10.39)		12.0(10.74)

Notes: 20 minutes, compare all drugs: p<0.0001
180 minutes, compare all drugs: p=0.021

FEV1, % change

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	5.7(6.93)		5.2(7.62)

Other Efficacy/Effectiveness Outcomes and Comments:

methacholaine challenge PC20
FEV1: Albuterol and Levabuterol at 20 min had greater effect than S-salbutamol and placebo (p NR); S-salbutamol NSD from placebo (p=0.10); all drugs NSD from placebo at 180 min

NR

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Cockcroft, 1997 — Quality rating (Efficacy, Safety): Fair, NA

Adverse Events:

DBP

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	68(5.89)	12	70(9.01)
12	67(10.05)	12	66(11.09)
	NR(NR)		NR(NR)

SBP

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	110(6.93)	12	108(9.35)
12	115(7.27)	12	110(9.35)
	NR(NR)		NR(NR)

DBP

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	68(5.89)	12	70(9.01)
12	67(10.05)	12	66(11.09)
	NR(NR)		NR(NR)

SBP

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	110(6.93)	12	108(10.05)
12	107(6.24)	12	109(3.96)
	NR(NR)		NR(NR)

Heart rate

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	72.6(9.7)	12	71.3(9.35)
12	84.0(11.09)	12	84.1(8.66)
	NR(NR)		NR(NR)

Heart rate

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	72.6(9.7)	12	71.3(9.35)
12	76.6(NR)	12	75.4(9.7)
	NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Cockcroft, 1997 — Quality rating (Efficacy, Safety): Fair, NA

Restlessness, number with any reported

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	0(NR)	12	0(NR)
12	11(92)	12	11(92)
	NR(NR)		NR(NR)

Restlessness, number with any reported

Albuterol 2.5mg		Levalbuterol 1.25mg	
12	0(NR)	12	0(NR)
12	2(17)	12	3(25)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

PR increase for racemic salb & R-salbutamon @ 20min (p<0.0001); NSD for other drugs at 20 & 180min. BP: NSD any drug.
Restlessness: increase for racemic salb & lev at 20min (p<0.01); NSD for others at 180min; most restlessness was severe

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Datta, 2003 — Quality rating (Efficacy, Safety): Fair, Good

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	30	NR /	NR /	30

Inclusion criteria:

A clinical diagnosis of COPD; an FEV1 between 45% and 70% of predicted, and an FEV1/FVC ratio < 0.70; stable disease, as indicated by the absence of a clinical exacerbation and no change in COPD medications in the preceding month; the ability of patients

Exclusion criteria:

A clinical diagnosis of asthma; any coexisting medical problem that might interfere with the conduct of the study or place the patient at risk by participating.

Comments:

Population: **Mean age:** 69 years
Gender: 16.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg	single dose	30	69 years	16.67% Female
Levalbuterol 1.25mg	single dose	30	69 years	16.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

Oxygen saturation

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	-0.26(NR)		0.36(NR)

FVC

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	3.16(NR)		2.74(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Datta, 2003 — Quality rating (Efficacy, Safety): Fair, Good

FEV1

Albuterol 2.5mg		Levalbuterol 1.25mg	
30	1.15(0.49)	30	1.15(0.49)
30	NR(NR)	30	NR(NR)
	1.97(NR)		2.16(NR)

Albuterol vs Levalbuterol, p value: >0.05

Oxygen saturation

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	-0.63(NR)		-0.03(NR)

FVC

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	3.5(NR)		2.5(NR)

FEV1

Albuterol 2.5mg		Levalbuterol 1.25mg	
30	1.15(0.49)	30	1.15(0.49)
30	NR(NR)	30	NR(NR)
	1.99(NR)		1.78(NR)

Albuterol vs Levalbuterol, p value: >0.05

Oxygen saturation

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	0.13(NR)		0.30(NR)

FVC

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	0.05(NR)		-0.7(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Datta, 2003 — Quality rating (Efficacy, Safety): Fair, Good

FEV1

Albuterol 2.5mg		Levalbuterol 1.25mg	
30	1.15(0.49)	30	1.15(0.49)
30	NR(NR)	30	NR(NR)
	0.43(NR)		0.17(NR)

Albuterol vs Levalbuterol, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	2.5(NR)		3.7(NR)

Heart rate

Albuterol 2.5mg		Levalbuterol 1.25mg	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	5.5(NR)		5.6(NR)

Albuterol 2.5mg vs Placebo, p value: <0.01

Levalbuterol 1.25mg vs Placebo, p value: <0.01

Heart rate

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	1(NR)		2(NR)

Tremor, 0=no tremor; 6=severe tremor

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	0.50(NR)		0.30(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Datta, 2003 **Quality rating (Efficacy, Safety): Fair, Good**

Tremor, 0=no tremor; 6=severe tremor

Albuterol 2.5mg		Levalbuterol 1.25mg	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	0.46(NR)		0.26(NR)

Albuterol 2.5mg vs Placebo, p value: >0.05

Levalbuterol 1.25mg vs Placebo, p value: >0.05

Tremor, 0=no tremor; 6=severe tremor

Albuterol		Levalbuterol	
30	NR(NR)	30	NR(NR)
30	NR(NR)	30	NR(NR)
	0.43(NR)		0.30(NR)

Albuterol 2.5mg vs Placebo, p value: >0.05

Levalbuterol 1.25mg vs Placebo, p value: >0.05

Other Adverse Events and Comments:

There were no siginificant group differences.

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Gawchik, 1999 — Quality rating (Efficacy, Safety): Poor, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	43	10 /	5 /	33

Inclusion criteria:

Ages 2 and 11 years with a history of asthma for 6 months or more, a resting FEV1 between 50% and 80% of predicted normal (Polgar's) values, 3 consecutive FEV1 values that varied by less than 10%, and reversibility of 12% or more within 30 minutes after 2

Exclusion criteria:

If they had an upper or lower respiratory infection within 15 days of the baseline visit; were taking theophylline, methyphenidate hydrochloride, monoamine oxidase inhibitors, or trycyclic antidepressants; received anitbiotic treatment within 72 hours of

Comments:

Patterson's squares require that at least 14 subjects per age group complete the study for the squares to be balanced for carry-over and for the planned analysis to be performed. Therefore data from the 6- ro 11-year-old group was used in the efficacy ana

Population: **Mean age:** 8.3 years
Gender: 48.84% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 1.25mg	ingle dose, 4 visit	43	8.3 years	48.84% Female
Albuterol 2.5mg	ingle dose, 4 visit	43	8.3 years	48.84% Female
Levalbuterol 0.16mg	ingle dose, 4 visit	43	8.3 years	48.84% Female
Levalbuterol 0.31mg	ingle dose, 4 visit	43	8.3 years	48.84% Female
Levalbuterol 0.63mg	ingle dose, 4 visit	43	8.3 years	48.84% Female
Levalbuterol 1.25mg	ingle dose, 4 visit	43	8.3 years	48.84% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEVs, AUC

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.2	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
	9.1(1.4)		9.5(1.3)		9.3(1.2)		9.8(1.3)		9.4(1.9)		10.3(1.1)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Gawchik, 1999 — Quality rating (Efficacy, Safety): Poor, Fair

FEV1, peak change

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.25	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
	0.35(0.19)		0.40(0.18)		0.39(0.19)		0.42(0.24)		0.41(0.22)		0.51(0.28)

Albuterol 1.25mg vs Levalbuterol 1.25mg, p value: 0.05 -0.055

Notes: There were no significant differences between treatment groups.

FEV1, peak % change

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.25	
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)	28	NR(NR)
	24.6(22.5)		27.9(16.2)		28.7(16.9)		30.6(19.3)		31.1(24.7)		36.8(22.5)

Other Efficacy/Effectiveness Outcomes and Comments:

Plasma levels

Main comparisons were to placebo group; there were "o significant differences between treatment groups…"

Adverse Events:

No. of patients reporting adverse events

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.2	
43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)
43	NR(NR)	43	NR(NR)	43	5(12)	43	1(2)	43	5(12)	43	2(5)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Heart rate, mean change

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.2	
20	NR(NR)	20	NR(NR)	23	NR(NR)	20	NR(NR)	22	NR(NR)	22	NR(NR)
20	NR(NR)	20	NR(NR)	23	NR(NR)	20	NR(NR)	22	NR(NR)	22	NR(NR)
	10.6(NR)		10.2(NR)		0.4(NR)		6.0(NR)		10.8(NR)		15.9(NR)

Glucose

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.2	
43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)
43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)
	16.2(NR)		19.6(NR)		14.8(NR)		-0.5(NR)		21.2(NR)		30.5(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Gawchik, 1999 **Quality rating (Efficacy, Safety): Poor, Fair**

K+

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.16mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.2	
43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)
43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)	43	NR(NR)
	-0.4(NR)		-0.6(NR)		-0.2(NR)		-0.2(NR)		-0.5(NR)		-0.5(NR)

Other Adverse Events and Comments:

Therapy was well tolerated; reported AEs mild or moderate severity. 22 pts (51.2%) reported 49 Aes, NSD across groups.
Study discontinuation: 5-asthma exacerbations; 4-protocol violations; 1-personal.

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Handley, 2000 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 20	0	/ 0	/ 20

Inclusion criteria:

Male and female nonsmoking patients with asthma aged 18-50 years. All eligible patients had mild tpersistent to moderate persistent asthma requiring at least weekly asthma medication, and demonstrated a resting and reporducible forced expiratory volume i

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 36 years
Gender: 75% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg	NR	20	36 years	75% Female
Levalbuterol 0.31mg	NR	20	36 years	75% Female
Levalbuterol 0.63mg	NR	20	36 years	75% Female
Levalbuterol 1.25mg	NR	20	36 years	75% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, duration of effect, at least 15% increased

Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
20	NR(NR)	20	NR(NR)	20	NR(NR)	20	NR(NR)
20	237(NR)	20	NR(NR)	20	221(NR)	20	275(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Calcium

FEV1:
- albuterol 2.5mg vs levalbuterol 1.25mg, p>0.05
Time to onset: all similar

Other Adverse Events and Comments:

The proportion of pts experiencing an AE. As well as the total number of AEs reported, was comparable across the five treatment groups (data not shown).
Nervousness, the most common AE:
- 5/7 in the levalbuterol 1.25mg group
- 3/6 in the albuterol 2.5mg group
There was a generak reduction as the dose of levalbuterol was reduced, but not reach statistical significance due to small sample size.

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Handley, 2000	Quality rating (Efficacy, Safety): Fair, Fair

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Hardasmalani, 2005 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Parallel **Run-in :** NA **Setting:** Emergency
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 70	0	/ 0	/ 63

Inclusion criteria:
Age 5-21 yrs; known history of asthma; presenting to ER with acute asthma exacerbation

Exclusion criteria:
Chronic cardiac, neurological or endocrinologic disorders; previous allergy to B2 agonists; previous participation in the study; patients who had received 2 or more treatments in past two hours ("treatments" not further specified)

Comments:
Although authors state that 70 patients "successfully completed" the study, post-study physiological data is provided for 63 patients. All other results presented as mean values, thus determining the # of patients is impossible.

Population: **Mean age:** 12.3 yrs years
Gender: 40% Female

Intervention:

Duration: 3 treatments, 1 hr

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg/3mL TID	q20min x3	34	13.03 yrs y	53% Female
Levalbuterol 1.25mg/3m T	q20min x3	36	11.33 yrs y	38% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

Respiratory rate

Albuterol 2.5mg/3mL TID		Levalbuterol 1.25mg/3m TIDL	
34	25.50(6.54)	36	26.40(7.19)
34	22.00(NR)	36	22.63(NR)
	-3.50(3.84)		-3.77(6.02)

Albuterol 2.5mg/3mL TID vs Levalbuterol 1.25mg/3m TIDL, p value: 0.83

Oxygen saturation rate

Albuterol 2.5mg/3mL TID		Levalbuterol 1.25mg/3m TIDL	
NR	96.82(2.24)	NR	96.53(2.26)
NR	98.23(NR)	NR	97.95(NR)
	1.41(1.76)		1.42(1.54)

Albuterol 2.5mg/3mL TID vs Levalbuterol 1.25mg/3m TIDL, p value: 0.99

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Hardasmalani, 2005 — Quality rating (Efficacy, Safety): Fair, NA

PEFR

Albuterol 2.5mg/3mL TID		Levalbuterol 1.25mg/3m TIDL	
NR	170.59(NR)	NR	166.94(NR)
NR	NR(NR)	NR	NR(NR)
	97.35(77.55)		95.14(63.06)

Albuterol 2.5mg/3mL TID vs Levalbuterol 1.25mg/3m TIDL, p value: 0.896

Effectiveness Outcomes:

Need for extra treatments

Albuterol 2.5mg/3mL TID		Levalbuterol 1.25mg/3m TIDL	
34	NR(NR)	36	NR(NR)
34	7(21)	36	5(14)
	NR(NR)		NR(NR)

Albuterol 2.5mg/3mL TID vs Levalbuterol 1.25mg/3m TIDL, p value: >0.05

Need for hospitalization

Albuterol 2.5mg/3mL TID		Levalbuterol 1.25mg/3m TIDL	
34	NR(NR)	36	NR(NR)
34	2(6)	36	3(8)
	NR(NR)		NR(NR)

Albuterol 2.5mg/3mL TID vs Levalbuterol 1.25mg/3m TIDL, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

NR

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Lotvall J 2001 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Laboratory
Country: Sweden

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	20	0 /	0 /	20

Inclusion criteria:
documented history of asthma, FEV1 of >=60% and >=15% reversibility after 400 ug nebulized RS-albuterol; current nonsmokers; no smoking for last 12m

Exclusion criteria:
Lower respiratory tract infection within 4w of entry; history of life-threatening asthmatic attachs, any concomitant illness.

Comments:
within 1w of study entry, patients could not take any albuterol-containing products of long-acting B2agonists; they were transferred to terbutaline for rescue treatment from screening to end of study.
Could take regular study medications at stable doses

Population: **Mean age:** 50 years
Gender: 40% Female

Intervention:

Duration: Multidose, single days

Drug name	Total daily dosage	N	Mean age	Gender
Levalbuterol 6.25 to 1600	cumulative	20	50 years	40% Female
Albuterol 12.5 to 3200 ug	cumulative	20	50 years	40% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, change from baseline at highest dosage

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	NR(NR)	20	NR(NR)
	0.664(0.36)		0.686(0.31)

Other Efficacy/Effectiveness Outcomes and Comments:

Placbeo and (S) only reported graphically, and were similar and less improvement in FEV1 than (R) and (RS)
QTc interval: both ® and (RS) albuterol produced dose-related increases, up to 0.05 seconds (data not shown).

Adverse Events:

Total adverse events

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	24(NR)	20	30(NR)
	NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Lotvall J 2001 **Quality rating (Efficacy, Safety): Fair, Fair**

Total B-2-mediated events

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	17(85)	20	20(100)
	NR(NR)		NR(NR)

Heart rate, change from baseline in highest dosage

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	NR(NR)	20	NR(NR)
	12.4(NR)		14.0(NR)

Palpitations

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	8(40)	20	7(35)
	NR(NR)		NR(NR)

Ventricular, tachyarrhythmias

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	2(10)	20	3(15)
	NR(NR)		NR(NR)

K+, change from baseline in highest dosage

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	NR(NR)	20	NR(NR)
	-0.26(NR)		-0.24(NR)

K+, change from baseline in highest dosage

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	NR(NR)	20	NR(NR)
	-0.26(NR)		-0.24(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Lotvall J 2001 — Quality rating (Efficacy, Safety): Fair, Fair

Tremor

Levalbuterol 6.25 to 1600 ug		Albuterol 12.5 to 3200 ug	
20	NR(NR)	20	NR(NR)
20	7(35)	20	9(45)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

The frequency & severity of AEs w/ R or RS-albuteral wer ecomparable (no p-value provided).

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Milgrom, 2001 **Quality rating (Efficacy, Safety): Fair, Good**

Design:

Study design: RCT DB Parallel **Run-in :** 7 days days **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	398 /	338	19 /	6 /	338

Inclusion criteria:

Male or female, aged 4 to 11 years; documented diagnosis of at least mild asthma for ≥60 days before screening; baseline FEV1 within 40% to 85% of predicted with ≥15% reversibility to RAC at screening.

Exclusion criteria:

Participation in an investigational study within 30 days of randomization; known sensitivity to study medications or their components; lower respiratory tract infection in the 2 weeks before randomization; clinically significant abnormality in the 12-lead

Comments:

Population: **Mean age:** 8.5 years
Gender: 41.72% Female

Intervention:

Duration: 3 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 1.25mg	tid	67	8.7 years	44.78% Female
Albuterol 2.5mg	tid	66	8.5 years	36.36% Female
Levalbuterol 0.31mg	tid	70	8.7 years	41.43% Female
Levalbuterol 0.63mg	tid	70	8.6 years	41.43% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, median peak %

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	24.2(NR)	66	26.7(NR)	70	27.0(NR)	70	25.4(NR)
65	22.3(NR)	60	27.6(NR)	64	24.9(NR)	69	25.7(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Effectiveness Outcomes:

Asthma, control days

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
NR	0(NR)	NR	NR(NR)	NR	1.6(NR)	NR	0.25(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Levalbuterol 0.31mg vs Levalbuterol 0.63mg, p value: <0.04

Albuterol 1.25mg vs Levalbuterol 0.31mg, p value: <0.04

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Milgrom, 2001 **Quality rating (Efficacy, Safety): Fair, Good**

Other Efficacy/Effectiveness Outcomes and Comments:

Pharmacokinetic parameters: CK/F, T1/2, AUC(ng*hr/ml), Cmax(ng/ml)

Day 0, there wre significant more patients responding to levalbuterol 0.31mg (62.9%) than to albuterol 1.25mg (41.8%), p=0.012 immediately after treatment.
NSD among treatment groups for overall asthma symptom assessment score, symptom-free days, and quality of life score (data not shown).
NSD asthma control days among groups day 0-14.

Adverse Events:

Overall

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
NR	NR(34.3)	NR	NR(51.5)	NR	NR(42.9)	NR	NR(52.9)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Heart rate, day 21, change

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
65	NR(NR)	60	NR(NR)	64	NR(NR)	69	NR(NR)
	NR(NR)		6.0(NR)		0.2(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 0.31mg, p value: <0.001

Notes: Levabuterol 0.31mg produced significant smaller changes than all other active treatments (p<0.02). In adidtion, 35% of subjects on al 2.5mg had clinically significant tachycardia (define as >= 15bpm increase on heart rate, and 35% had an heart rate >= 100 bpm at least once albuterol 2.5mg. This compared with approcimately 20% for all other active treatments.

Heart rate, day 1, change

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
	NR(NR)		11.3(NR)		0.7(NR)		NR(NR)

Albuterol 2.5mg vs Levalbuterol 0.31mg, p value: <0.001

K+, % pts w/level decreased >= 0.8mEq/ml, day 0

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.31mg		Levalbuterol 0.63mg	
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
67	NR(NR)	66	NR(NR)	70	NR(NR)	70	NR(NR)
	7(NR)		25(NR)		5(NR)		6(NR)

Other Adverse Events and Comments:

AEs included fever, headache, asthma, pharyngitis, & rhinitis. QTc: lev 0.31mg, alb 2.5mg caused a significantly greater prolongation of the QTc on day0 (p<0.001), day21 (p=0.054). Glucose: alb 2.5mg caused significant larger increases than lev 0.31mg & lev 0.63mg (p=<0.043), alb 1.25mg on day21 (p<0.003).
Potassium: Decrease in K+ greater in albuterol 2.5 mg than levalbuterol 0.63 & 0.31 (p<0.05)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Nelson, 1998; Pleskow, 2004 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Parallel **Run-in :** 7 days days **Setting:** NR
Country: US

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	424	362	34	0	362

Inclusion criteria:

Nonsmoking males or females 12 years of age or older who had at least a 6-month history of chronic and stable asthma (as defined by the American Thoracic Society) requiring pharmacotherapy. Patients were eligible if they had moderate-to severe lung compro

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 36.5 years
Gender: 60% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 1.25mg TID	tid	68	37.9 years	39.71% Female
Albuterol 2.5mg TID	tid	74	38.3 years	48.65% Female
Levalbuterol 0.63mg TID	tid	72	36.2 years	50% Female
Levalbuterol 1.25mg TID	tid	73	35.0 years	34.25% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, predicted

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	60.06(7.57)	74	58.98(7.46)	72	58.89(7.74)	73	60.09(8.09)
68	81.14(13.26)	74	80.03(14.29)	72	82.48(13.82)	73	83.64(13.30)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1, predicted

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	60.06(7.57)	74	58.98(7.46)	72	58.89(7.74)	73	60.09(8.09)
68	79.87(13.22)	74	79.24(14.12)	71	81.89(13.11)	73	83.54(13.36)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Nelson, 1998; Pleskow, 2004 **Quality rating (Efficacy, Safety): Fair, Fair**

FEV1, predicted

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	60.06(7.57)	74	58.98(7.46)	72	58.89(7.74)	73	60.09(8.09)
68	80.27(13.96)	74	79.59(13.95)	71	82.78(13.75)	73	83.93(13.70)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1, predicted

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	60.06(7.57)	74	58.98(7.46)	72	58.89(7.74)	73	60.09(8.09)
68	71.93(13.82)	74	72.46(16.08)	70	74.07(14.30)	72	78.18(14.38)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
24	0.6(NR)	35	0.82(NR)	31	0.78(NR)	35	0.92(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1, predicted

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	60.06(7.57)	74	58.98(7.46)	72	58.89(7.74)	73	60.09(8.09)
60	66.08(14.19)	67	67.89(15.15)	63	68.22(16.04)	68	72.63(14.36)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Effectiveness Outcomes:

% of patients using any rescue medication

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	66(97.1)	74	72(97.3)	72	69(95.8)	73	70(95.9)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

No. of puffs of rescue medication puffs per day

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	3.59(NR)	74	4.3(NR)	72	3.75(NR)	73	3.44(NR)
68	3.6(3.0)	74	3.8(2.9)	72	3.5(3.2)	73	2.7(2.5)
	0.01(NR)		-0.5(NR)		-0.25(NR)		-0.74(NR)

Albuterol 1.25mg TID vs placebo, p value: 0.12

Albuterol 2.5mg TID vs placebo, p value: 0.42

Levalbuterol 0.63mg TID vs placebo, p value: 0.006

Levalbuterol 1.25mg TID vs placebo, p value: <0.0001

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Nelson, 1998; Pleskow, 2004 **Quality rating (Efficacy, Safety): Fair, Fair**

Asthma, increase

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg		Placebo TID	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)	75	NR(NR)
68	2(2.9)	74	2(2.7)	72	1(1.4)	73	3(4.1)	75	2(2.7)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Asthma

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	5(7.4)	74	6(8.1)	72	5(6.9)	73	4(5.5)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Albuterol 1.25mg vs Levalbuterol 0.63mg, p value: NR

Albuterol 1.25mg vs Levalbuterol 1.25mg, p value: NR

Albuterol 2.5mg vs Levalbuterol 0.63mg, p value: NR

Albuterol 2.5mg vs Levalbuterol 1.25mg, p value: NR

Other Efficacy/Effectiveness Outcomes and Comments:

FEV1: Levalbuterol 0.63 and albuterol 2.5 mg had similar peak improvements and duration of action at weeks 0,2,4
FEV1: comparing combined levalbuterol treatments and combined albuterol treatments, levalbuterol increased more in FEV1, p=0.006.

Adverse Events:

Serious adverse events

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	1(1.5)	74	1(1.4)	72	3(4.2)	73	1(1.4)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

No. of patients with any adverse events

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	14(20.6)	74	20(27.0)	72	12(16.7)	73	23(31.5)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Heart rate increase

Albuterol 2.5mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	2.3(NR)		4.9(NR)

Albuterol 2.5mg TID vs Levalbuterol 0.63mg TID, p value: <0.05

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Nelson, 1998; Pleskow, 2004 **Quality rating (Efficacy, Safety): Fair, Fair**

Tachycardia

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	0(0)	74	2(2.7)	72	2(2.8)	73	2(2.7)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Mean serum glucose

Levalbuterol 0.63mg TID		Albuterol 2.5mg TID	
72	NR(NR)	74	NR(NR)
NR	NR(NR)	NR	NR(NR)
	2.4(NR)		4.9(NR)

Albuterol 2.5mg TID vs Levalbuterol 0.63mg TID, p value: >0.05

Notes: NSD between groups

Change in mean K+

Levalbuterol 0.63mg TID		Albuterol 2.5mg TID	
72	NR(NR)	74	NR(NR)
NR	NR(NR)	NR	NR(NR)
	-0.2(NR)		-0.3(NR)

Albuterol 2.5mg TID vs Levalbuterol 0.63mg TID, p value: >0.05

Leg cramps

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	0(0)	74	0(0)	72	0(0)	73	2(2.7)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Headache

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	2(2.9)	74	2(2.7)	72	3(4.2)	73	4(5.5)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Dizziness

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	0(0)	74	0(0)	72	1(1.4)	73	2(2.7)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Nelson, 1998; Pleskow, 2004 **Quality rating (Efficacy, Safety): Fair, Fair**

Anxiety

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	0(0)	74	0(0)	72	0(0)	73	2(2.7)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Nervousness

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	3(4.4)	74	6(8.1)	72	2(2.8)	73	7(9.6)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Tremor

Albuterol 1.25mg		Albuterol 2.5mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg	
68	NR(NR)	74	NR(NR)	72	NR(NR)	73	NR(NR)
68	0(0)	74	2(2.7)	72	0(0)	73	5(6.8)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

Med well tolerated, w/ 22.9% pts reporting potentially drug-related AEs, NSD across groups (p=0.18). Most commom AEs reported were asthma-related, nervousness, headache, tremor & tachycardia. Nervousness/tremor: 0.63mg lev+1.25mg alb < 1.25mg lev+ 2.5mg alb, p=0.003; 0.63mg lev vs 2.5mg alb, p=0.098
HR: levalbuterol 0.63mg & albuterol 1.25mg demostrated a similar increase in HR (ranging from 3.6 to 4.9 bpm, p=0.24); levalbuterol 0.63mg had significant lower HR than albuterol 2.5mg, p=<0.03. Serious AEs: lev 0.63: 3 pts; lev 1.25: 1 pt; albuterol 1.25: 1 pt; albuterol 2.5: 1

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Qureshi, 2005 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Emergency
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	651 /	139 /	139	10 /	2 /	129

Inclusion criteria:

Children who were between the ages of 2 and 14 years, had a known history of asthma, and presented to the pediatric ED with an acute asthma exacerbation associated with an initial clinical asthma score greater than 8 or a forced expiratory volume in 1 se

Exclusion criteria:

Use of ipratropium or levalbuterol within 24 hours of presentation to the ED, use of oral or parenteral steroids within the past week, use of inhaled steroids greater than 400 mg per day of beclomethasone or its equivalent in the last week, history of chr

Comments:

Population: **Mean age:** 5.8 years
Gender: 34.11% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5-5mg	in X3, then q30-6	64	5.5 years	48.44% Female
Levalbuterol 1.25-2.5mg	in X3, then q30-6	65	6 years	20% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

Pulse oximetry, median change

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	NR(NR)	65	NR(NR)
	1(NR)		-1(NR)

Albuterol vs Levalbuterol, p value: >0.05

Effectiveness Outcomes:

% of patients hospitalized after ER visit

Albuterol 2.5-5mg		Levalbuterol 1.25-2.5mg	
64	NR(NR)	65	NR(NR)
64	13(NA)	65	11(NA)
	NR(NR)		NR(NR)

Albuterol vs Levalbuterol, p value: >0.05

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Qureshi, 2005 — Quality rating (Efficacy, Safety): Fair, Fair

Length of care (median)

Albuterol 2.5-5mg		Levalbuterol 1.25-2.5mg	
64	NR(NR)	65	NR(NR)
64	125(NR)	65	121(NR)
	NR(NR)		NR(NR)

Albuterol vs Levalbuterol, p value: >0.05

No. of nebulizations, median

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	3(NR)	65	3(NR)
	NR(NR)		NR(NR)

Albuterol vs Levalbuterol, p value: >0.05

Respiratory rate, median change

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	NR(NR)	65	NR(NR)
	-4(NR)		-5(NR)

Albuterol vs Levalbuterol, p value: >0.05

Asthma score, % change from baseline

Albuterol 2.5-5mg		Levalbuterol 1.25-2.5mg	
17	NR(NR)	16	NR(NR)
17	NR(NR)	16	NR(NR)
	NR(NR)		NR(NR)

Albuterol 2.5-5mg vs Levalbuterol 1.25-2.5mg, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

Enantiomer concentration

NR

Adverse Events:

Other adverse events

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	1(2)	65	1(2)
	NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Qureshi, 2005 **Quality rating (Efficacy, Safety): Fair, Fair**

Pulse rate, median change

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	NR(NR)	65	NR(NR)
	18(NR)		18(NR)

Albuterol vs Levalbuterol, p value: >0.05

Nausea and vomitting

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	11(17)	65	5(8)
	NR(NR)		NR(NR)

K+, drop of <3.0 meq/L

Albuterol		Levalbuterol	
9	NR(NR)	9	NR(NR)
NR	3(5)	NR	3(5)
	NR(NR)		NR(NR)

Headache

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	4(6)	65	8(12)
	NR(NR)		NR(NR)

Notes: NSD between groups

Light-headedness

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	3(5)	65	9(14)
	NR(NR)		NR(NR)

Notes: NSD between groups

Tremor

Albuterol		Levalbuterol	
64	NR(NR)	65	NR(NR)
64	21(33)	65	24(37)
	NR(NR)		NR(NR)

Notes: NSD between groups

Other Adverse Events and Comments:

Serum K+: 18 pts (9 alb, 9 lev); decreased below 3.0 meq/L: 3 alb, 3 lev; none showed any concurrent clinical or cardiac

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Qureshi, 2005	Quality rating (Efficacy, Safety): Fair, Fair

rhythm abnormality; 2 rechecked next day & both >4 meq/L. Tachycardia>200 beats/min (1 alb pt); elevated temp (1 lev pt).

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Ramsay, 1999 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: New Zealand

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	0 /	0 /	22

Inclusion criteria:

forced expiratory volume in 1 s (FEV1) greater than 65% predicted and BHR to MCh (pro-vocative concentration causing a 20% fall in FEV1 (PC20) <8 mg/ml [12]) demonstrated within 1 year of enrolment.

Exclusion criteria:

smokers or ex-smokers whose consumption exceeded 5 pack years; asthma exacerbations during the 12 weeks prior to enrolment; subjects taking concomitant medications, e.g. long-acting beta-agonists, antihistamines, theophylline; and medical conditions that

Comments:

Population: **Mean age:** 39.4 years
Gender: 72.73% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	22	39.4 years	72.73% Female
Levalbuterol 100ug	NR	22	39.4 years	27.27% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol		Levalbuterol	
22	2.58(0.83)	22	2.55(0.79)
22	2.82(0.80)	22	2.84(0.78)
	NR(NR)		NR(NR)

FEV1

Albuterol		Levalbuterol	
22	2.58(0.83)	22	2.55(0.79)
22	2.83(0.80)	22	2.81(0.76)
	NR(NR)		NR(NR)

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Ramsay, 1999 — Quality rating (Efficacy, Safety): Fair, NA

FEV1

Albuterol		Levalbuterol	
22	2.58(0.83)	22	2.55(0.79)
22	2.73(0.82)	22	2.72(0.82)
	NR(NR)		NR(NR)

FEV1

Albuterol		Levalbuterol	
22	2.58(0.83)	22	2.55(0.79)
22	2.80(0.82)	22	2.83(0.81)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

PC20AMP

NR

Other Adverse Events and Comments:

NR

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Skoner, 2005 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Parallel **Run-in :** 1 wk days **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	408 /	NR /	211	35 /	NR /	NR

Inclusion criteria:

Children 2-5 yrs with diagnosis of asthma for at least 30 days, in good health, with no chronic medical conditions, thoracic radiograph withresults suggesting no other pulmonary disorder

Exclusion criteria:

Treatment with an investigational drug or systemic corticosteroid within 30 days or astemizole use within 90 days of screening; respiratory tract infection within 2 wks of study entry; life-threatening asthma within previous year. No concomitant beta2-ago

Comments:

Analyses based on "ITT" population. For safety, this is clearly stated as being 211 pts. For efficacy/effectiveness, no actual number of patients is specified.

Population: **Mean age:** 3.4 years
Gender: 69.24% Female

Intervention:

Duration: 3 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 1.25mg-2.5mg T	3.75 - 7.5mg	52	3.4 years	36.54% Female
Levalbuterol 0.31mg TID	.93mg	58	3.4 years	29.31% Female
Levalbuterol 0.63mg TID	1.89mg	51	3.3 years	31.37% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Effectiveness Outcomes:

Pediatric Asthma Caregiver's QOL Questionnaire

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID		Placebo	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	0.33(1.20)		0.61(1.10)		0.74(0.96)		0.19(1.04)

Notes: Authors report minimum clinically significant improvement in both lev groups, but not albuterol or placebo; NSD among groups; for pts <33lbs, change in PACQLQ was greater for lev 0.31 and 0.63 than albuterol (p<0.02)

Child Heatlh Status Questionnaire score

Notes: All groups showed improvement in scores, NSD among groups (p>0.05)

Functional Status Questionnaire

Notes: All groups showed improvement in scores, NSD among groups (p>0.05)

Use of rescue medication

Notes: Decreased use of rescue medications by pts in all treatment groups; NSD among groups

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Skoner, 2005 **Quality rating (Efficacy, Safety): Fair, Fair**

Uncontrolled asthma days

Notes: Relative to baseline, all treatment groups reported decrease in number of uncontrolled asthma days (defined as 2+ dosesof rescue medication/day). No further data provided by authors. NSD among groups

Pediatric Asthma Questionnaire - mean change

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	-1.5(NR)		-2.2(NR)		-1.5(NR)

Notes: Mean change values interpolated from graph. NSd among groups

Pediatric Asthma Questionnaire - mean change

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	-2.0(NR)		-2.9(NR)		-2.4(NR)

Notes: Mean change values interpolatd from graph. NSD among groups

Pediatric Asthma Questionnaire - mean change

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	-2.9(4.1)		-3.5(3.1)		-3.3(4.3)

Notes: Mean change values and SD values presented in text (other timepoints interpolated from graph). NSD among groups

Other Efficacy/Effectiveness Outcomes and Comments:

Efficacy outcomes not abstracted include: plasma (s-) and (r-) albuterol concentrations and PEF

Authors conducted some subgroup analysis based on pts <33 and > or = 33 lbs. The only time significance was reached was in comparison PACQLQ score for pts >33lbs in favor of levalbuterol:
mean change 0.82 (SD1.2) for levalbuterol 0.31mg and 1.08 (SD 0.97) for levalbuterol 0.63mg compared to 0.10 (SD 1.01) for albuterol (p=0.08 albuterol vs levalbuterol 0.31; p=0.016 albuterol vs levalbuerol 0.63)

Adverse Events:

% of pts experiencing any AE

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID		Placebo	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(53.8)	NR	NR(53.4)	NR	NR(60.8)	NR	NR(52)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Notes:

Mean change after 30 min

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	3.6(8.9)		0.4(14.1)		3.4(11.0)

Notes:

Evidence Table 4. Albuterol vs levalbuterol - RCTs: efficacy and safety

Skoner, 2005 — Quality rating (Efficacy, Safety): Fair, Fair

Mean change after 30 min

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
	5.5(11.0)		2.3(11.0)		6.0(10.7)

Notes:

Number of patients reporting

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	0(NR)	NR	1(NR)	NR	0(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes:

Hyperkinesia (number of pts reporting)

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	1(NR)	NR	0(NR)	NR	1(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes:

Serious asthma AE (number of patients reporting)

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	1(NR)	NR	0(NR)	NR	0(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes:

Asthma exacerbation (number of pts reporting)

Albuterol 1.25mg-2.5mg TID		Levalbuterol 0.31mg TID		Levalbuterol 0.63mg TID	
NR	NR(NR)	NR	NR(NR)	NR	NR(NR)
NR	2(NR)	NR	1(NR)	NR	1(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes:

Other Adverse Events and Comments:

All pts had decrease in K+ and glucose 30-60min after last dose at day 21 (data not shown).

Evidence Table 5. Albuterol vs metaproterenol - RCTs: efficacy and safety

Berezuk, 1983 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	11	1 /	NR /	10

Inclusion criteria:
Clinical history of reversible COPD verified by a pre-qualification visit

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 59.5 years
Gender: 0% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 180ug	180ug	11	59.5 years	0% Female
Metaproterenol 1300ug	1300ug	11	59.5 years	0% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

"Area under the curve for % change in FEV1, FEF25-75 and FVC vs time for each treatment condition:"
FEV1: albuterol 315.40 (SD 155.43); metaproterenol 316.97 (SD 98.22);
FEF25-75: albuterol 328.61 (SD 166.46); metaproterenol 274.19 (SD 158.18)
FVC: albuterol 353.43 (SD 198.59); metaproterenol 378.19 (SD 213.86)

Actual FEV, FEF and FVC % changes reported only in graphical form, no quantitative data provided.

Adverse Events:

Minor, see comments

NR NR(NR)
NR NR(NR)
NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 5. Albuterol vs metaproterenol - RCTs: efficacy and safety

Berkowitz, 1986 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 18	0	/ NR	/ 18

Inclusion criteria:
Documented, exercise-induced bronchospasm with treadmill challenge prestudy

Exclusion criteria:
NR

Comments:
Before treatment washout: 8 hrs for all medications, 24 hours for long-acting theophylline

Population: **Mean age:** 14.5 years
Gender: 61.11% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	0.18mg	18	14.5 years	61.11% Female
Metaproterenol	1.30mg	18	14.5 years	61.11% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, decrease over time

Albuterol		Metaproterenol	
18	NR(NR)	18	NR(NR)
18	NR(NR)	18	NR(NR)
	15.5(16.6)		28.0(19.7)

FEV1

Albuterol		Metaproterenol	
18	87.7(12.3)	18	87.1(11.03)
18	96.6(5.09)	18	97.5(7.21)
	8.9(NR)		10.4(NR)

Albuterol vs Metaproterenol, p value: NR

FEV1, decrease over time

Albuterol		Metaproterenol	
18	NR(NR)	18	NR(NR)
18	NR(NR)	18	NR(NR)
	2.7(7.8)		5.5(7.8)

Evidence Table 5. Albuterol vs metaproterenol - RCTs: efficacy and safety

Berkowitz, 1986 **Quality rating (Efficacy, Safety): Fair, NA**

Other Efficacy/Effectiveness Outcomes and Comments:

Mean workload for exercise challenges:
albuterol: 2.49 W/kg (SE 0.08, SD 0.32, range 1.78-3.29)
metaproterenol: 2.50 W/kg (SE 0.07, SD 0.30, range 1.86-3.08)

Albuterol appeared to have longer duration of effect (mean 2-4hrs) compared to metaproterenol (<2hrs)

Other Adverse Events and Comments:

NR

Evidence Table 6. Albuterol vs pirbuterol - RCTs: efficacy and safety

Beumer, 1980; Beumer 1979 **Quality rating (Efficacy, Safety): Poor, Poor**

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** NR

Country: Netherland

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	12	0 /	0 /	12

Inclusion criteria:

Outpatients aged 18-65 years, who had given informed consetn, were selected. All had asthma found to respond on one day in the week preceeding the study (evaluation day) to two successive inhalations of 100ug slbutamol from a metered aerosol with an impr

Exclusion criteria:

Excluded were patients with clinically relevant hematological, rnal, hepatic, metabolic or cardiovascular disease; those in whom the use of beta-adrenergic drug was contraindicated; patients receiving any other investigational drug and pregnant women.

Comments:

Population: **Mean age:** 57.6 years

Gender: 0% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	12	57.6 years	0% Female
Pirbuterol 200ug	NR	12	57.6 years	0% Female
Pirbuterol 400ug	NR	12	57.6 years	0% Female
Pirbuterol 600ug	NR	12	57.6 years	0% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1 at least 25% increase, no. of pts

Albuterol 200ug		Pirbuterol 200ug		Pirbuterol 400ug		Pirbuterol 600ug	
12	NR(NR)	12	NR(NR)	12	NR(NR)	12	NR(NR)
12	10(83.3)	12	10(83.3)	12	9(75)	12	9(75)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

FEV1

Albuterol 200ug		Pirbuterol 200ug		Pirbuterol 400ug		Pirbuterol 600ug	
12	1.04(NR)	12	1.22(NR)	12	1.12(NR)	12	1.11(NR)
12	1.46(NR)	12	1.43(NR)	12	1.46(NR)	12	1.52(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Evidence Table 6. Albuterol vs pirbuterol - RCTs: efficacy and safety

Beumer, 1980; Beumer 1979 **Quality rating (Efficacy, Safety): Poor, Poor**

FVC

Albuterol 200ug		Pirbuterol 200ug		Pirbuterol 400ug		Pirbuterol 600ug	
12	2.25(NR)	12	2.57(NR)	12	2.31(NR)	12	2.54(NR)
12	3.03(NR)	12	2.96(NR)	12	3.01(NR)	12	3.14(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Albuterol 200ug vs Pirbuterol 200ug, p value: <0.05

Other Efficacy/Effectiveness Outcomes and Comments:

Maximum expiratory flow rate
Maximum breathing capacity
FEV3

No significant difference between pirtuterol 400mcg, 600mcg and albuterol in any analysis; and that pirbuterol 200mcg was inferior to each of the three other active treatments in some of the comparisons, depending on the pulmonary function test concerned.

Other Adverse Events and Comments:

No side effects were reported during the study.
There were no abnormalities in laboratory test results of any clinical relevance. The only abnormalities were was high SGPT values before & after treatment in almost all pts.
Mean PR & BPs fell slightly & to ab similar ectent after all treatments. All ECG's were normal

Evidence Table 6. Albuterol vs pirbuterol - RCTs: efficacy and safety

Volkl, 1991 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT NR Crossover **Run-in :** NR **Setting:** NR

Country: Germany

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	17	0 /	0 /	17

Inclusion criteria:

Male or female patients aged between 6 and 12 years suffering from manifest airways obstruction (with reduced FEV1) for whom therapy with a beta2-sympathomimetic agent was medically indicated. The children included suffered without exception from the exo

Exclusion criteria:

Patients without any experience in the use of inhalers - either MDI or powder inhalers - were excluded from the study. Patients who clearly deviated from normal perceptive ability, determined in a foregoing clinical assessment, or who had an acurte lung

Comments:

Population: **Mean age:** 9.8 years

Gender: 47.06% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.1mg	NR	17	9.8 years	47.06% Female
Pirbuterol 0.2mg	NR	17	9.8 years	52.94% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF

Albuterol 0.1mg		Pirbuterol 0.2mg	
17	NR(NR)	17	NR(NR)
17	NR(NR)	17	NR(NR)
	32(NR)		44(NR)

Albuterol 0.1mg vs Pirbuterol 0.2mg, p value: 0.13

FVC

Pirbuterol 0.2mg		Albuterol 0.1mg	
17	NR(NR)	17	NR(NR)
17	NR(NR)	17	NR(NR)
	35(NR)		24(NR)

Albuterol 0.1mg vs Pirbuterol 0.2mg, p value: 0.97

Evidence Table 6. Albuterol vs pirbuterol - RCTs: efficacy and safety

Volkl, 1991 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1

Albuterol 0.1mg		Pirbuterol 0.2mg	
17	NR(NR)	17	NR(NR)
17	NR(NR)	17	NR(NR)
	30(NR)		47(NR)

Albuterol 0.1mg vs Pirbuterol 0.2mg, p value: 0.036

Symptoms typical of beta2-sympathomimetics

Albuterol 0.1mg		Pirbuterol 0.2mg	
17	0(NR)	17	0(NR)
17	0(NR)	17	0(NR)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

The linear analusis of the crossover effects showed a significant treatment effect for the relative increase in FEV1 (10 min after application) (p=0.02) and no period effect (p=0.217), or interaction (p=0.602). For FVC, the treatment effect was near the significant level of 5% (p=0.081).

Adverse Events:

Cardiac side effect

Albuterol 0.1mg		Pirbuterol 0.2mg	
17	0(NR)	17	0(NR)
17	0(NR)	17	0(NR)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 7. Metaproterenol vs pirbuterol - RCTs: efficacy and safety

Chodosh, 1989 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 26	2	/ 0	/ 24

Inclusion criteria:

> 18 yrs
COPD responsive to standard bronchodilator aerosol therapy as evidenced by at least 15% improvement in FEV1 following 2 inhalations of isoproterenol

Exclusion criteria:

Pregnancy
Evidence of significant hematologic, renal, hepatic or cardiac disease or seizure disorder
Existing diabetes, hypertension or heart disease (beta-agonists contraindicated)
Post-randomization exclusion: pts who did not demonstrate at least 15%

Comments:

No beta-agonist sympathomimetric bronchodilators or other investigational drugs allowed
Washout of theophylline, corticosteroids, and cromolyn at 12 hrs prior to treatment; all aerosols at 6 hrs

Population: **Mean age:** 57 years
Gender: 50% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Metaproterenol	NR	26	57 years	50% Female
Pirbuterol 0.2mg	NR	26	57 years	50% Female
Pirbuterol 0.4mg	NR	26	57 years	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

MMEF

Pirbuterol 0.2mg		Pirbuterol 0.4mg		Metaproterenol	
26	NR(NR)	26	NR(NR)	26	NR(NR)
26	NR(NR)	26	NR(NR)	26	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: MMEF only expressed as p values:
0.2 mg pirbuterol: p greater than/equal to 0.01
0.4 mg pirbuterol: p greater than/equal to 0.05
1.3 mg metaproterenol: pirbuterol: p greater than/equal to 0.05

Evidence Table 7. Metaproterenol vs pirbuterol - RCTs: efficacy and safety

Chodosh, 1989 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1, median peak % increase

Pirbuterol 0.2mg		Pirbuterol 0.4mg		Metaproterenol	
26	NR(NR)	26	NR(NR)	26	NR(NR)
26	NR(NR)	26	NR(NR)	26	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Author indicates that both pirbuterol doses, but not metaproterenol, were statistically significant from placebo (p<0.05)

FEV1, % of responders

Pirbuterol 0.2mg		Pirbuterol 0.4mg		Metaproterenol	
26	NR(NR)	26	NR(NR)	26	NR(NR)
26	NR(NR)	26	NR(NR)	26	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: % of responders at unspecified (likely variable) tmepoints:
0.2 pirbuterol - 62.5%
0.4 pirbuterol - 46%
metaproterenol - 37.5%

Other Efficacy/Effectiveness Outcomes and Comments:

AUC

FEV1 response = three consecutive readings exceeding 15% increase over baseline
Maximum midexpiratory flow rate (MMEF) response = three consecutive readings exceeding 20% increase over baseline

Adverse Events:

Diverse, non-serious adverse events

Metaproterenol		Pirbuterol	
26	NR(NR)	26	NR(NR)
26	4(15.4)	25	3(12)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

3/25 pirbuterol self-reported: dizziness, blurred vision, itching, rash.
4/26 metaproterenol self-reported: chest pain/tightness/pressure, headache
No discontinuations due to Aes

Evidence Table 7. Metaproterenol vs pirbuterol - RCTs: efficacy and safety

Tinkelman, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 1 week days **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	133	NR /	NR /	118

Inclusion criteria:

>18 yrs
met American Thoraz Soc. criteria for asthma
min. 15% reversibility in FEV1 following isoproterenol

Exclusion criteria:

NR

Comments:

Washout prior to treatment: 6 hrs for conventional bronchodilator therapy, 12 hrs for sustained action bronchodilator therapy. Author's analysis showed study adequately powered (90% chance) to detect statistically significant mean deterioration in peak

Population: **Mean age:** 45 years
Gender: 56.39% Female

Intervention:

Duration: 12 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Metaproterenol	NR	66	44 years	57.58% Female
Pirbuterol	NR	67	46 years	55.22% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

Response defined as greater than 15% from baseline
Quantitative values not reported (only presented in graphical form as area under the curve.) Authors report that only outcome measure which approached statistical significance was in favor of pibuterol for FEV1 (p=0.06)

Adverse Events:

Tachycardia

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	2(3.0)	66	2(3.0)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Evidence Table 7. Metaproterenol vs pirbuterol - RCTs: efficacy and safety

Tinkelman, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Diarrhea

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	1(1.5)	66	2(3.0)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Nausea

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	1(1.5)	66	4(6.1)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Dry mouth

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	2(3.0)	66	2(3.0)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Headache

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	3(4.5)	66	3(4.5)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Dizziness

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	0(0)	66	2(3.0)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Evidence Table 7. Metaproterenol vs pirbuterol - RCTs: efficacy and safety

Tinkelman, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Nervousness

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	7(10.4)	66	14(21.2)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Drowsiness

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	2(3.0)	66	1(1.5)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Tremor

Metaproterenol		Pirbuterol	
67	NR(NR)	66	NR(NR)
67	2(3.0)	66	3(4.5)
	NR(NR)		NR(NR)

Notes: value = n of patients reporting AE

Other Adverse Events and Comments:

p<= .05 for all AEs; 42% of pirb, 31% of meta. Infreq. AEs: personality change; hyperkinesia, chest pain/tightness; abdom. pain/cramps; glossitis; stomatitis; bruising; weakness; paresthesia; palpitations; appetite increase; flatulence; rash; fatigue /malaise; hoarseness

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Asher, 1985 **Quality rating (Efficacy, Safety): Fair, NA**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: New Zealand

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	25	0 /	0 /	25

Inclusion criteria:

Children with frequent episodic asthma in stable condition

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 6.6 years

Gender: 40% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.2mg	NR	25	6.6 years	40% Female
Fenoterol 0.2mg	NR	25	6.6 years	40% Female

Outcomes:

Reporting of data is as follows:

Drug Name

n Baseline

n Follow-up

Mean Difference

Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.2mg		Fenoterol 0.2mg	
25	1.19(NR)	25	1.16(NR)
25	1.28(NR)	25	1.27(NR)
	NR(19)		NR(12)

Notes: Baseline values = FEV1 as % of predicted value

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Blackhall, 1976 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT SB Parallel **Run-in :** NR **Setting:** NR

Country: Australia

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 30	NR	/ NR	/ NR

Inclusion criteria:

Reversible airway obstruction
Ability to perform respiratory function tests (not further specified)
Baseline FEV1 at least 2SD below their predicted normal value

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 9.8 years
Gender: 50% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2mg	2mg	10	NR	50% Female
Fenoterol 2mg	2mg	10	NR	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC

Albuterol 2mg		Fenoterol 2mg	
NR	1.72(NR)	NR	1.75(NR)
NR	2.14(NR)	NR	2.16(NR)
	0.42(NR)		0.41(NR)

Notes: Follow up indicates increase from baseline

FEV1

Albuterol 2mg		Fenoterol 2mg	
NR	1.19(NR)	NR	1.19(NR)
NR	1.70(NR)	NR	1.73(NR)
	0.51(NR)		0.54(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Blackhall, 1976 — Quality rating (Efficacy, Safety): Fair, Fair

Adverse Events:

Pulse rate

Albuterol 2mg	Fenoterol 2mg
NR 89.5(NR)	NR 92.7(NR)
NR 99.9(NR)	NR 101.6(NR)
10.4(NR)	8.9(NR)

Notes: Follow up indicates increase from baseline

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Dawson, 1985 — Quality rating (Efficacy, Safety): Good, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: New Zealand

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	40	0 /	0 /	40

Inclusion criteria:
Children with chronic asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 8.9 years
Gender: 45% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	40	8.9 years	45% Female
Fenoterol 200ug	NR	40	8.9 years	45% Female
Albuterol 400ug	NR	40	8.9 years	45% Female
Fenoterol 400ug	NR	40	8.9 years	45% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR, % increase from baseline

Albuterol 400ug (Rotahaler)		Fenoterol 200ug (Rotahaler)		Albuterol 400ug (Inhalator)		Fenoterol 200ug (Inhalator)	
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
	59(NR)		45(NR)		67(NR)		68(NR)

FVC, % increase from baseline

Albuterol 400ug (Rotahaler)		Fenoterol 200ug (Rotahaler)		Albuterol 400ug (Inhalator)		Fenoterol 200ug (Inhalator)	
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
	28(NR)		18(NR)		35(NR)		31(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Dawson, 1985 — Quality rating (Efficacy, Safety): Good, Fair

FEV1, % increased from baseline

Albuterol 400ug (Rotahaler)		Fenoterol 200ug (Rotahaler)		Albuterol 400ug (Inhalator)		Fenoterol 200ug (Inhalator)	
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
	51(NR)		35(NR)		50(NR)		45(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Authors report that only outcome measures which attained significance were for mean % FEV1 scores in favor of albuterol ($p<0.02$) and % FVC scores, also in favor of albuterol ($p<0.10$)

Adverse Events:

Heart rate, % increase from baseline

Albuterol 400ug (Rotahaler)		Fenoterol 200ug (Rotahaler)		Albuterol 400ug (Inhalator)		Fenoterol 400ug (Inhalator)	
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
40	NR(NR)	40	NR(NR)	40	NR(NR)	40	NR(NR)
	-2(NR)		2(NR)		6(NR)		0(NR)

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Graff-Lonnevig, 1976 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Outpatient clinic
Country: Sweden

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	16	NR /	NR /	NR

Inclusion criteria:
Children with chronic asthma with manifest bronchial obstruction.

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 10.4 years
Gender: 6.25% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	200ug	16	10.4 years	6.25% Female
Fenoterol 100ug	100ug	16	10.4 years	6.25% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC, % change from baseline

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	19(NR)		15(NR)

Notes: Figures interpolated from graph in text.

FEV1, % change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	29(NR)		24(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Graff-Lonnevig, 1976 **Quality rating (Efficacy, Safety): Fair, Fair**

FVC, % change from baseline

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	12(NR)		13(NR)

Notes: Figures interpolated from graph in text.

FEV1, % change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	21(NR)		21(NR)

Notes: Figures interpolated from graph in text.

FVC, % change from baseline

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	13(NR)		15.5(NR)

Notes: Figures interpolated from graph in text.

FEV1, % change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	18(NR)		19(NR)

Notes: Figures interpolated from graph in text.

FVC, % change from baseline

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	13(NR)		11(NR)

Notes: Figures interpolated from graph in text.

FVC, % change from baseline

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	16(NR)		9(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Graff-Lonnevig, 1976 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, % change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	20(NR)		16(NR)

Notes: Figures interpolated from graph in text.

Other Efficacy/Effectiveness Outcomes and Comments:

Figures interpolated from graph in text.

Adverse Events:

Heart rate, mean change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	-3.8(NR)		-3.9(NR)

Notes: Figures interpolated from graph in text.

Heart rate, mean change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	-3.7(NR)		-8.2(NR)

Notes: Figures interpolated from graph in text.

Heart rate, mean change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	-2.0(NR)		-5.7(NR)

Notes: Figures interpolated from graph in text.

Heart rate, mean change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	2.1(NR)		1.7(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Graff-Lonnevig, 1976 — Quality rating (Efficacy, Safety): Fair, Fair

Heart rate, mean change

Albuterol 200ug		Fenoterol 100ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	-8.0(NR)		-6.8(NR)

Notes: Figures interpolated from graph in text.

Other Adverse Events and Comments:

Measure of change of HR unclear in text - only reported as "change in HR." Assume this is in bpm.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Hanley, 1979 — Quality rating (Efficacy, Safety): Poor, NA

Design:

Study design: RCT NR NR **Run-in :** NR **Setting:** Hospital, patients admitted for testin
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 28	NR	/ 9	/ 19

Inclusion criteria:
Asthmatic patients who had established diurnal asthma patterns as demonstrated by 4-hourly peak expiratory flow rates (PEFR)

Exclusion criteria:
NR

Comments:
Patients whose values at 12:00am differed by <10% of the respective mean baseline on the night they received salbutamol and fenoterol were excluded from analysis (post-randomization exclusions)

Population: **Mean age:** NR years
Gender: NR% Female

Intervention:

Duration: 2 puffs overnight

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	200ug	NR	NR	NR
Fenoterol 200ug	400ug	NR	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR

Albuterol 100ug		Fenoterol 200ug	
24	331(NR)	24	331(NR)
19	339(NR)	19	363(NR)
	8(NR)		32(NR)

PEFR

Albuterol 100ug		Fenoterol 200ug	
24	331(NR)	24	331(NR)
19	236(NR)	19	284(NR)
	-95(NR)		-47(NR)

Effectiveness Outcomes:

Preference on waking, based on patient assessment

Albuterol 100ug	
24	NR(NR)
19	2(NR)
	NR(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Hanley, 1979			Quality rating (Efficacy, Safety): Poor, NA	
	Fenoterol 200ug		No preference	
	24	NR(NR)	24	NR(NR)
	19	7(NR)	19	10(NR)
		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Patient assessment of asthma severity on waking:
10 patients: albuterol = fenoterol
7 patients: favored fenoterol
2 patients: favored albuterol
(p<0.15)

NR

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Hockley, 1983 — Quality rating (Efficacy, Safety): Poor, Poor

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 10	NR	/ NR	/ 10

Inclusion criteria:
Adult asthmatics

Exclusion criteria:
NR

Comments:
Single-dose study

Population: **Mean age:** 50 years
Gender: 60% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 5mg	5mg	10	50 years	60% Female
Fenoterol 5mg	5mg	10	50 years	60% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	3.21(NR)	10	3.40(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FEV1

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	2.15(NR)	10	2.35(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Hockley, 1983 **Quality rating (Efficacy, Safety): Poor, Poor**

FVC

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	3.13(NR)	10	3.33(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FEV1

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	2.13(NR)	10	2.30(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FVC

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	3.0(NR)	10	3.21(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FEV1

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	1.94(NR)	10	2.28(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FVC

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	2.70(NR)	10	2.78(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

FEV1

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	1.7(NR)	10	1.67(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Hockley, 1983 — Quality rating (Efficacy, Safety): Poor, Poor

Other Efficacy/Effectiveness Outcomes and Comments:

Efficacy measures only provided in graphical form. Authors state that FEV1 and FVC were both "significantly lower" with salbutamol vs fenoterol at 8 hrs (final timepoint of study)

Adverse Events:

SBP

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	129(NR)	10	122(NR)
	NR(NR)		NR(NR)

Palpitations

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	0(0)	10	1(10)
	NR(NR)		NR(NR)

Notes: Value = # of patients reporting AE

Tremor

Albuterol 5mg		Fenoterol 5mg	
10	NR(NR)	10	NR(NR)
10	1(10)	10	2(20)
	NR(NR)		NR(NR)

Notes: Value = # of patients reporting AE

Other Adverse Events and Comments:

Systolic BP only AE outcome noted as being "significant".

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Holt, 1983 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT Open Crossover **Run-in :** NR **Setting:** NR
Country: Norway

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 17	0	/ 6	/ 11

Inclusion criteria:
Children with bronchial asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 11.7 years
Gender: 27.27% Female

Intervention:

Duration: 3 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.075mg/kg	up to 4x/day	11	11.7 years	27.27% Female
Fenoterol 0.2mg	up to 3x/day	11	11.7 years	27.27% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR, % of predicted rate

Albuterol 0.075mg/kg	Fenoterol 0.2mg
11 69.5(NR)	11 67.3(NR)
11 89.5(NR)	11 86.5(NR)
NR(NR)	NR(NR)

PEFR, % of predicted rate

Albuterol 0.075mg/kg	Fenoterol 0.2mg
11 69.5(NR)	11 67.3(NR)
11 89.4(NR)	11 86.6(NR)
NR(NR)	NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

Serious side effects were not observed.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Huhti, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Finland

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 12	0	/ 0	/ 12

Inclusion criteria:

On the day preceding the tests, FEV1 had to demonstrate an increase of 20% or more after 2 inhalations of isoproterenol (isoprenaline) from a standard-sized aerosol canister (a total of 0.16 mg of isoproterenol)

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 46 years

Gender: 66.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.1mg	0.2mg	12	46 years	66.67% Female
Fenoterol 0.2mg	0.4mg	12	46 years	66.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	3.28(1.11)	12	3.29(1.28)
12	3.82(0.38)	12	3.82(0.35)
	0.54(NR)		0.53(NR)

PEFR, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	204(79.67)	12	211(90.07)
12	302(55.43)	12	308(69.28)
	98(NR)		97(NR)

FEV1, mean increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	1.47(0.45)	12	1.58(0.69)
12	2.15(0.45)	12	2.31(0.55)
	0.68(NR)		0.73(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Huhti, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

FVC, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	3.28(1.11)	12	3.29(1.28)
12	3.84(0.35)	12	3.85(0.35)
	0.56(NR)		0.53(NR)

PEFR, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	204(79.67)	12	211(90.07)
12	292(51.96)	12	291(62.35)
	88(NR)		80(NR)

FEV1, mean increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	1.47(0.45)	12	1.58(0.69)
12	2.09(0.45)	12	2.30(0.52)
	0.62(NR)		0.72(NR)

FVC, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	3.28(1.11)	12	3.29(1.28)
12	3.78(0.38)	12	3.84(0.38)
	0.50(NR)		0.55(NR)

PEFR, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	204(79.67)	12	211(90.07)
12	312(55.43)	12	311(72.75)
	83(NR)		100(NR)

FEV1, mean increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	1.47(0.45)	12	1.58(0.69)
12	2.14(0.52)	12	2.34(0.55)
	0.67(NR)		0.76(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Huhti, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

FVC, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	3.28(1.11)	12	3.29(1.28)
12	3.52(0.38)	12	3.72(0.38)
	0.24(NR)		0.43(NR)

PEFR, increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	204(79.67)	12	211(90.07)
12	238(55.43)	12	291(65.82)
	34(NR)		80(NR)

FEV1, mean increase from baseline

Albuterol 0.1mg		Fenoterol 0.2mg	
12	1.47(0.45)	12	1.58(0.69)
12	1.88(0.55)	12	2.15(0.52)
	0.41(NR)		0.57(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Efficacy outcomes reported following TWO doses of intervention

Adverse Events:

Heart rate, mean increase

Albuterol 0.1mg		Fenoterol 0.2mg	
12	93(13.86)	12	90(10.39)
12	87(6.93)	12	95(6.93)
	-6(NR)		5(NR)

Notes: p<0.001 for degree of significance b/t fenoterol and albuterol by paired t-test

Heart rate, mean increase

Albuterol 0.1mg		Fenoterol 0.2mg	
12	93(13.86)	12	90(10.39)
12	90(10.39)	12	93(6.93)
	-3(NR)		3(NR)

Notes: p<0.05 for degree of significance b/t fenoterol and albuterol by paired t-test

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Huhti, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Heart rate, mean increase

Albuterol 0.1mg		Fenoterol 0.2mg	
12	93(13.86)	12	90(10.39)
12	85(10.39)	12	93(10.39)
	-8(NR)		3(NR)

Notes: p<0.001 for degree of significance b/t fenoterol and albuterol by paired t-test

Heart rate, mean increase

Albuterol 0.1mg		Fenoterol 0.2mg	
12	93(13.86)	12	90(10.39)
12	90(6.93)	12	89(10.39)
	-3(NR)		-1(NR)

Notes: p<0.001 for degree of significance b/t fenoterol and albuterol by paired t-test

Other Adverse Events and Comments:

AEs reported following TWO doses of intervention.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Konig, 1985 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: RCT DB Crossover **Run-in :** **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	24	NR /	NR /	NR

Inclusion criteria:

Adult asthmatics with mild airway obstruction at the time of the trial (FEV1 less than 80% of expected) and the reversibility of obstruction documented previously by an increase of at least 15% in FEV1 after 2 puffs of isoproterenol (160 ug).

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 28.7 years
Gender: 16.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 180ug	360ug	24	28.7 years	16.67% Female
Fenoterol 320ug	640ug	24	28.7 years	16.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, % change

Albuterol 180ug		Fenoterol 320ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text

FEV1, % change

Albuterol 180ug		Fenoterol 320ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Konig, 1985 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1, Bronchodilation in , % of peak value

Albuterol 180ug		Fenoterol 320ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	86.7(NR)		89.6(NR)

Notes: Peak bronchodilation for both interventions occurred at 1 hour.

FEV1, % change

Albuterol 180ug		Fenoterol 320ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text

FEV1, % change

Albuterol 180ug		Fenoterol 320ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

AEs reported by 11 fenoterol pts: tremor, headache, dizziness. No AEs reported by albuterol pts. Authros report no statistically significant changes in HR or BP for either drug.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Maesen, 1984 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT DB Crossover **Run-in :** **Setting:** NR

Country: Netherlands

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	20	/	/	/

Inclusion criteria:

Stable, reversible bronchial obstruction; a basic FEV1 of at least 1 litre and less than 70% of the predicted normal value

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 40.4 years

Gender: 40% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.4mg	NR	20	40.4 years	40% Female
Fenoterol 0.2mg	NR	20	40.4 years	40% Female

Outcomes:

Reporting of data is as follows:

Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	5.37(NR)	20	5.41(NR)
20	7.20(NR)	20	7.31(NR)
	1.83(NR)		1.90(NR)

FEV1, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	2.15(NR)	20	2.15(NR)
20	2.87(NR)	20	2.83(NR)
	.72(NR)		.68(NR)

FVC, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	3.55(NR)	20	3.52(NR)
20	4.21(NR)	20	4.09(NR)
	.66(NR)		.57(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Maesen, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

PEFR, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	5.37(NR)	20	5.41(NR)
20	6.77(NR)	20	6.67(NR)
	1.40(NR)		1.26(NR)

FEV1, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	2.15(NR)	20	2.15(NR)
20	2.69(NR)	20	2.72(NR)
	.54(NR)		.57(NR)

FVC, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	3.55 L(NR)	20	3.52 L(NR)
20	4.02 L(NR)	20	3.98 L(NR)
	.47(NR)		.46(NR)

PEFR, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	5.37(NR)	20	5.41(NR)
20	7.35(NR)	20	7.18(NR)
	1.98(NR)		1.77(NR)

FEV1, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	2.15(NR)	20	2.15(NR)
20	2.87(NR)	20	2.84(NR)
	.72(NR)		.69(NR)

FVC, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	3.55(NR)	20	3.52(NR)
20	4.25(NR)	20	4.12(NR)
	.70(NR)		.60(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Maesen, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

PEFR, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	5.37(NR)	20	5.41(NR)
20	6.94(NR)	20	7.03(NR)
	1.57(NR)		1.62(NR)

FEV1, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	2.15(NR)	20	2.15(NR)
20	2.81(NR)	20	2.79(NR)
	.66(NR)		.64(NR)

FVC, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	3.55(NR)	20	3.52(NR)
20	4.11(NR)	20	4.06(NR)
	.56(NR)		.54(NR)

PEFR, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	5.37(NR)	20	5.41(NR)
20	6.30(NR)	20	6.51(NR)
	.93(NR)		1.10(NR)

FEV1, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	2.15(NR)	20	2.15(NR)
20	2.56(NR)	20	2.61(NR)
	.41(NR)		.46(NR)

FVC, mean increase from baseline

Albuterol 0.4mg		Fenoterol 0.2mg	
20	3.55(NR)	20	3.52(NR)
20	3.86(NR)	20	3.92(NR)
	.31(NR)		.40(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

No statistically significant differences found between study drugs for FEF25-75.

All values interpolated from graphs in text

Other Adverse Events and Comments:

Authors report no significant changes in PR or BP.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Maesen, 1984	Quality rating (Efficacy, Safety): Fair, Fair

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: Romania

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	63	0 /	0 /	63

Inclusion criteria:
Chronic bronchitis (CIBA Guest Symposium and American Thoriacic Society criteria); a response of the FEV1 of at least 10% of baseline values 30 minutes after inhalation of 1500 ug orciprenaline aerosol

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 56.5 years
Gender: 25.4% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	63	56.5 years	25.4% Female
Terbutaline 500ug	NR	63	56.5 years	25.4% Female
Fenoterol 400ug	NR	63	56.5 years	25.4% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	0.325(NR)		0.305(NR)		0.285(NR)

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Effectiveness Outcomes:

Preference

Albuterol 400ug		Terbutaline 500ug		Fenoterol 400ug		No preference	
63	NR(NR)	63	NR(NR)	63	NR(NR)	63	NR(NR)
63	19(30.2)	63	16(25.4)	63	21(33.3)	63	7(11.1)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

VC

NR

Other Adverse Events and Comments:

No significant changes in HR.
No significant changes in BP.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Newhouse, 1994 — Quality rating (Efficacy, Safety): Fair, Fair/poor

Design:

Study design: RCT DB Crossover **Run-in :** **Setting:** NR

Country: Canada

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	12	0 /	0 /	12

Inclusion criteria:

Adults with American Thoracic Society-defined asthma who had been stable for a least 4 weeks. Prior to entry into the study S had to show a 15% or greater improvement in FEV1 within 30 minutes after inhaling two puffs (400ug) of fenoterol from a MDI.

Exclusion criteria:

Patients with known cardiac arrhythmias or sinus tachycardia and those with known hypersensitivity to sympathomimetic compounds were excluded, as were smokers, lactating or pregnant women, and those of child-bearing potential not using an approved birth c

Comments:

Population: **Mean age:** 52.2 years

Gender: 75% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2500ug	2500ug	12	52.2 years	75% Female
Fenoterol 2500ug	2500ug	12	52.2 years	75% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 2500ug		Fenoterol 2500ug	
12	1.52(0.38)	12	1.55(0.42)
12	2.18(0.52)	12	2.25(0.55)
	0.66(NR)		0.70(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Newhouse, 1994 — Quality rating (Efficacy, Safety): Fair, Fair/poor

Heart rate

Albuterol 2500ug		Fenoterol 2500ug	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	-6(NR)		NR(NR)

Other Adverse Events and Comments:

AEs reported as follows: no significant AEs for either intervention. One report of headache/dizziness by a sabutamol patient. Reported changes in HR & BP pooled for both interventions.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Newhouse, 1996 — Quality rating (Efficacy, Safety): Good, Good

Design:

Study design: RCT DB Parallel **Run-in :** **Setting:** Emergency

Country: Canada

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	1,038	257	257	0	1	256

Inclusion criteria:

Acutely ill asthmatic patients presenting to the ED with acute severe asthma (FEV1 less than 50% of predicted); 18 to 45 years of age inclusive, had a diagnosis of asthma according to American Thoracic Society Criteria, had a pretreatment FEV1 of 50% or

Exclusion criteria:

Patients ``in extremis" requiring immediate therapy or therapy other than oxygen, methylprednisolone, and beta2-agonists were excluded from the study as were patients with significant complicating or concomitant medical illnesses (eg, pneumonia, acute my

Comments:

Population: **Mean age:** 29.4 years

Gender: 54.09% Female

Intervention:

Duration: Multidose, 1 day

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	up to 1600ug	129	28.9 years	58.14% Female
Fenoterol 200ug	up to 3200ug	128	29.9 years	50% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 100 microgram		Fenoterol 200 microgram	
256	1.25(1.6)	256	1.16(1.6)
256	NR(NR)	256	NR(NR)
	0.59(NR)		0.75(NR)

Albuterol 100 microgram vs Fenoterol 200 microgram, p value: NR

Notes: Effect difference most pronounced at max dose of 1,600 microgram albuterol and 3,200 microgram fenoterol (estimated from graph: 1.0 L albuterol vs 1.4 L fenoterol)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

DBP

Albuterol 100 microgram		Fenoterol 200 microgram	
256	78.3(NR)	256	81.0(NR)
256	NR(NR)	256	NR(NR)
	4.7(NR)		2.4(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Newhouse, 1996 **Quality rating (Efficacy, Safety): Good, Good**

Notes: Mean change indicates a DECREASE in diastolic BP

SBP

Albuterol 100 microgram		Fenoterol 200 microgram	
256	123.1(NR)	256	128.4(NR)
256	NR(NR)	256	NR(NR)
	2.9(NR)		5.9(NR)

Notes: Mean change indicates a DECREASE in systolic BP

Heart rate

Albuterol 100 microgram		Fenoterol 200 microgram	
256	96.5(NR)	256	96.7(NR)
256	NR(NR)	256	NR(NR)
	3.3(NR)		2.9(NR)

Notes: Mean change value indicates DECREASE in pulse rate during curse of intervention

Tremor

Albuterol 100 microgram		Fenoterol 200 microgram	
256	10(NR)	256	20(NR)
256	25(NR)	256	51(NR)
	NR(NR)		NR(NR)

Notes: For albuterol, 23 pts reported 25 events; fenoterol 48 pts reported 51 events

Other Adverse Events and Comments:

Other AEs reported include headache & dizziness. No figures on # of pts were provided by authors. AE rate was 43% vs 56% (p=0.029) for albuterol & fenoterol respectively. 84% of AEs associated w/ cumulative doses of >8 puffs regardless of intervention.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Scalabrin, 1996 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Parallel **Run-in :** **Setting:** NR
Country: Brazil

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	21	NR	NR	21

Inclusion criteria:
Children presenting with acute bronchial asthma and demonstrated an FEV1 lower than 80% of nromal predicted value.

Exclusion criteria:
Children should not have taken long-acting theophylline, antihistamines, or corticosteroids for 24 hr and beta-adrenergic agents or other bronchodilator medication for 12 hr before the study.

Comments:

Population: **Mean age:** 10.41 years
Gender: 42.86% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 5mg	NR	11	NR	NR
Fenoterol 0.083mg/kg	NR	14	NR	NR
Terbutaline 0.1mg/kg	NR	12	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 1.04(0.53)	21 1.18(0.50)	21 0.94(0.44)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Scalabrin, 1996 Quality rating (Efficacy, Safety): Fair, Fair

FEV1, mean % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Bronchodilator effect, mean duration

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg			
21	NR(NR)	21	NR(NR)	21	NR(NR)	21	NR(NR)
21	365(NR)	21	287(NR)	21	NR(NR)	21	285(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Figures interpolated from graph in text.

Adverse Events:

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.
3/11 (27%) of albuterol patients had larger HR increases (36, 60 and 70 bpm respectively); 2/14 (14%) of fenoterol patients had larger heart r increases (38 & 60 bpm)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Scalabrin, 1996 — Quality rating (Efficacy, Safety): Fair, Fair

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
93(NR)	86(NR)	104(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
106(NR)	34(NR)	90(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
151(NR)	93(NR)	62(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
175(NR)	167(NR)	119(NR)

Notes: Figures interpolated from graph in text.

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Sturani, 1983 **Quality rating (Efficacy, Safety): Fair, NA**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Italy

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

NR / NR / 12 NR / NR / 12

Inclusion criteria:

Patients who showed a fall in FEV1 of more than 15% after exercise on two separate occasions.

Exclusion criteria:

NR

Comments:

Short-acting bronchodilators wash-out 12 hrs; long-acting wash-out 24 hrs

Population: **Mean age:** 23 years

Gender: 41.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.2mg 2 puffs	0.4 mg	12	23 years	41.67% Female
Fenoterol 0.4mg 2 puffs	0.8 mg	12	23 years	41.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean increase from baseline

Albuterol 0.2mg		Fenoterol 0.4mg	
12	3.041(0.745)	12	3.031(0.744)
12	NR(NR)	12	NR(NR)
	NR(6.7)		NR(7.2)

Notes: Comparison also made between immediate pre-exercise and post exercise: inhibitory effect better after fenoterol than salbumamol (p<0.025)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Suissa, 1994 **Quality rating (Efficacy, Safety): NA, Good**

Design:

Study design: Cohort NA NA **Run-in :** NA **Setting:** NR

Country: Canada

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NA /	NA /	NA	NA /	NA /	12,301

Inclusion criteria:

Cohort of pts. who received asthma prescriptions at least 10 times between 1978-1987.

Exclusion criteria:

NR

Comments:

Population: **Mean age:** NR years

Gender: NR% Female

Intervention:

Duration: Case control NR

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	NR (variable)	NR	NR	NR
Fenoterol	NR (variable)	NR	NR	NR

Outcomes:

Reporting of data is as follows:

Drug Name

n Baseline

n Follow-up

Mean Difference

Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Death, asthma, beta agonist use vs non-use

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	NR(NR)		NR(NR)

Albuterol use vs non-use, p value: NR

Fenoterol use vs non-use, p value: NR

Notes: Mean diff. value = adjusted rate difference in death/10,000 asthmatics/year

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Suissa, 1994 **Quality rating (Efficacy, Safety): NA, Good**

Death, non-asthma related

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	28.7(NR)	NR	21.4(NR)
	NR(NR)		NR(NR)

Notes: Values represent absolute rate of non-asthma related deaths/10,000 asthmatics/year
albuterol 95% CI: -7.8, 11.6
fenoterol 95% CI: -22.8, 8.5
Rate difference b/t use and non-use:
albuterol: 1.9/10,000/year
fenoterol: -7.2/10,000/year

Death, asthma-related

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	9.8(NR)	NR	61.5(NR)
	NR(NR)		NR(NR)

Notes: Values represent absolute rates of asthma death/10,000 asthmatics/year
albuterol 95% CI: -5.2, 6.2
fenoterol 95% CI: 31.1, 81.5
Rate difference b/t use and non-use:
albuterol - 0.5/10,000/year
fenoterol - 56.3/10,000/year

Other Adverse Events and Comments:

More frequent use of drugs associated w/ higher death rates; after adjusting for dose-equivalence (20,000ug/mo., using quad. dose-response curve+adjusted rates); quad. coeff. for the sq. of the dose: alb 3.1 (CI 1.1-5.1) vs fen 5.9 (CI 2.9-8.9), p=0.4

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tandon, 1980 — Quality rating (Efficacy, Safety): Fair, Fair/Poor

Design:

Study design: RCT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: Australia

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	15	0	0	15

Inclusion criteria:
COPD, using bronchodilators at the time of the study

Exclusion criteria:
NR

Comments:
All patients had previously undergone pulmonary function testing in study setting and were familiar with lab and personnel

Population: **Mean age:** 52.5 years
Gender: 6.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	1,100ug	15	52.5 years	6.67% Female
Fenoterol 160ug	1,120ug	15	52.5 years	6.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

No values reported for % improvement in FEV1 folowing drug administration, however authors report no SS difference between interventions. No other efficacy outcomes reported.

Adverse Events:

Side effects

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	5(33)	15	13(87)
	NR(NR)		NR(NR)

Heart rate, change from baseline

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	-2(NR)		NR(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tandon, 1980 **Quality rating (Efficacy, Safety): Fair, Fair/Poor**

Heart rate, change from baseline

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	NR(NR)		9(NR)

Heart rate, change from baseline

Fenoterol 160ug		Albuterol 100ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	6.25(NR)		NR(NR)

Heart rate, change from baseline

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	-2.5(NR)		NR(NR)

Heart rate, change from baseline

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	NR(NR)		7.25(NR)

Heart rate, change from baseline

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	NR(NR)	15	NR(NR)
	NR(NR)		8(NR)

Ventricular, dysrhythmia

Albuterol 100ug		Fenoterol 160ug	
15	NR(NR)	15	NR(NR)
15	0(0)	15	4(27)
	NR(NR)		NR(NR)

Notes: Dysrhythmias in fenoterol patients occurred at 7 puffs (n=2), 9 puffs (n=1) and 11 puffs (n=1)

Other Adverse Events and Comments:

HR change from baseline only reported when change reached statistical significance; HR change is reported for albuterol at 1 & 3 puffs only, & for fenoterol at 7-13 puffs.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tang, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** Research Center
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 24	0	/ 0	/ 24

Inclusion criteria:
Patients with reversible airways obstruction (chronic bronchitis and asthma)

Exclusion criteria:
Women of child-bearing age

Comments:

Population: **Mean age:** 59.6 years
Gender: 20.83% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	200ug	24	59.6 years	20.83% Female
Fenoterol 100ug	200ug	24	59.6 years	20.83% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR

Albuterol 100ug	Fenoterol 100ug
NR 263(NR)	NR 260(NR)
NR 317(NR)	NR 311(NR)
54(NR)	51(NR)

PEFR

Albuterol 100ug	Fenoterol 100ug
NR 263(NR)	NR 260(NR)
NR 306(NR)	NR 305(NR)
43(NR)	45(NR)

PEFR

Albuterol 100ug	Fenoterol 100ug
NR 263(NR)	NR 260(NR)
NR 299(NR)	NR 299(NR)
36(NR)	39(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tang, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

PEFR

Albuterol 100ug		Fenoterol 100ug	
NR	263(NR)	NR	260(NR)
NR	310(NR)	NR	310(NR)
	47(NR)		50(NR)

PEFR

Albuterol 100ug		Fenoterol 100ug	
NR	263(NR)	NR	260(NR)
NR	274(NR)	NR	271(NR)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

DBP

Albuterol 100ug		Fenoterol 100ug	
24	79.6(13.72)	24	80.6(10.29)
24	76.4(9.8)	24	79.0(14.21)
	3.2(NR)		1.6(NR)

SBP

Albuterol 100ug		Fenoterol 100ug	
24	135.3(24.98)	24	129.5(20.58)
24	126.3(19.6)	24	124.0(21.56)
	-9.0(NR)		-5.5(NR)

DBP

Albuterol 100ug		Fenoterol 100ug	
24	79.6(13.72)	24	80.6(10.29)
24	78.1(7.84)	24	79.0(10.29)
	-1.5(NR)		-1.6(NR)

SBP

Albuterol 100ug		Fenoterol 100ug	
24	135.3(24.98)	24	129.5(20.58)
24	128.6(19.6)	24	127.3(20.58)
	-6.7(NR)		-2.2(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tang, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

DBP

Albuterol 100ug		Fenoterol 100ug	
24	79.6(13.72)	24	80.6(10.29)
24	77.3(6.86)	24	78.8(12.74)
	-2.3(NR)		-1.8(NR)

SBP

Albuterol 100ug		Fenoterol 100ug	
24	135.3(24.98)	24	129.5(20.58)
24	131.5(23.03)	24	128.9(20.09)
	-3.8(NR)		-0.6(NR)

DBP

Albuterol 100ug		Fenoterol 100ug	
24	79.6(13.72)	24	80.6(10.29)
24	80.1(8.33)	24	76.3(11.76)
	-0.5(NR)		-4.3(NR)

SBP

Albuterol 100ug		Fenoterol 100ug	
24	135.3(24.98)	24	129.5(20.58)
24	129.5(19.6)	24	124.9(21.07)
	-5.8(NR)		-4.6(NR)

Pulse rate

Albuterol 100ug		Fenoterol 100ug	
24	92.0(13.23)	24	88.7(10.78)
24	88.3(12.74)	24	84.5(10.78)
	-3.7(NR)		-4.2(NR)

Pulse rate

Albuterol 100ug		Fenoterol 100ug	
24	92.0(13.23)	24	88.7(10.78)
24	89.0(12.25)	24	85.6(10.78)
	-3.0(NR)		-3.1(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Tang, 1984 — Quality rating (Efficacy, Safety): Fair, Fair

Pulse rate

Albuterol 100ug		Fenoterol 100ug	
24	92.0(13.23)	24	88.7(10.78)
24	88.3(13.23)	24	83.9(11.76)
	-3.7(NR)		-4.8(NR)

Pulse rate

Albuterol 100ug		Fenoterol 100ug	
24	92.0(13.23)	24	88.7(10.78)
24	87.5(12.74)	24	82.4(9.8)
	-4.5(NR)		-6.3(NR)

Tremor

Albuterol 100ug		Fenoterol 100ug	
24	2(8.3)	24	3(12.5)
24	5(20.8)	24	7(29.2)
	3(NR)		4(NR)

Notes: For albuterol patients, 4 had an increase in tremor while 1 had a decrease.

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Windom, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: New Zealand

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	12	NR /	NR /	12

Inclusion criteria:
Subjects with stable asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 27 years
Gender: 41.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	12	27 years	41.67% Female
Fenoterol 400ug	NR	12	27 years	41.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Albuterol 400ug		Fenoterol 400ug	
12	2.4(0.69)	12	2.4(1.04)
12	NR(NR)	12	NR(NR)
	0.6(NR)		0.6(NR)

Notes: Figures interpolated from graph in text.

FEV1, mean change

Albuterol 400ug		Fenoterol 400ug	
12	2.4(0.69)	12	2.4(1.04)
12	NR(NR)	12	NR(NR)
	0.4(NR)		0.6(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Windom, 1990 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, mean change

Albuterol 400ug		Fenoterol 400ug	
12	2.4(0.69)	12	2.4(1.04)
12	NR(NR)	12	NR(NR)
	0.2(NR)		0.3(NR)

Notes: Figures interpolated from graph in text.

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

SBP, mean change

Albuterol 400ug		Fenoterol 400ug	
12	118.7(7.27)	12	119.3(9.01)
12	NR(NR)	12	NR(NR)
	2.5(NR)		-1.5(NR)

SBP, mean change

Albuterol 400ug		Fenoterol 400ug	
12	118.7(7.27)	12	119.3(9.01)
12	NR(NR)	12	NR(NR)
	-5.0(NR)		-1.5(NR)

SBP, mean change

Albuterol 400ug		Fenoterol 400ug	
12	118.7(7.27)	12	119.3(9.01)
12	NR(NR)	12	NR(NR)
	-1.5(NR)		-2.6(NR)

Heart rate, mean change

Albuterol 400ug		Fenoterol 400ug	
12	61.8(9.01)	12	68.2(9.7)
12	NR(NR)	12	NR(NR)
	4.0(NR)		6.0(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Windom, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Heart rate, mean change

Albuterol 400ug		Fenoterol 400ug	
12	61.8(9.01)	12	68.2(9.7)
12	NR(NR)	2	NR(NR)
	2.0(NR)		-1.0(NR)

Notes: Figures interpolated from graph in text.

Heart rate, mean change

Albuterol 400ug		Fenoterol 400ug	
12	61.8(9.01)	12	68.2(9.7)
12	NR(NR)	12	NR(NR)
	-0.25(NR)		0.0(NR)

Notes: Figures interpolated from graph in text.

K+, plasma concentration, mean change

Albuterol 400ug		Fenoterol 400ug	
12	3.9(0.35)	12	3.9(0.35)
12	NR(NR)	12	NR(NR)
	-0.1(NR)		-0.5(NR)

K+, plasma concentration, mean change

Albuterol 400ug		Fenoterol 400ug	
12	3.9(0.35)	12	3.9(0.35)
12	NR(NR)	12	NR(NR)
	0.0(NR)		-0.1(NR)

K+, plasma concentration, mean change

Albuterol 400ug		Fenoterol 400ug	
12	3.9(0.35)	12	3.9(0.35)
12	NR(NR)	12	NR(NR)
	-0.1(NR)		-0.1(NR)

Other Adverse Events and Comments:

Figures interpolated from graph in text.

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Wong, 1990 — Quality rating (Efficacy, Safety): Fair, Good

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: UK

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	10	NR	NR	10

Inclusion criteria:
Asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** NR years
Gender: 20% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	2,600 ug	10	NR	20% Female
Fenoterol 200ug	5,200 ug	10	NR	20% Female
Terbutaline 250ug	6,500 ug	10	NR	20% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.63(NR)		0.76(NR)		0.63(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.98(NR)		1.05(NR)		1.10(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.87(NR)		1.10(NR)		0.92(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Wong, 1990 **Quality rating (Efficacy, Safety): Fair, Good**

Other Efficacy/Effectiveness Outcomes and Comments:

Mean area under the curve - within subject differences for fenoterol vs albuterol(SE) and terbutaline(SE):
FEV1 - fenoterol 1.77; albuterol -0.16 (0.15); terbutaline -0.08 (0.15)
Potassium concentration - fenoterol -0.82; albuterol 0.54 (0.17); terbutaline 0.33(0.18)

All values interpolated from graphs in text

Adverse Events:

Heart rate, mean maximum change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	8(9)		29(24)		8(14)

Palpitations

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	1(10)	10	3(30)	10	3(30)
	NR(NR)		NR(NR)		NR(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.10(NR)		0.06(NR)		0.03(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.42(NR)		-0.73(NR)		-0.45(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.01(NR)		-0.42(NR)		-0.20(NR)

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Wong, 1990 — Quality rating (Efficacy, Safety): Fair, Good

Headache

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	3(30)	10	5(50)	0	2(20)
	NR(NR)		NR(NR)		NR(NR)

Tremor

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	4(40)	10	6(60)	10	4(40)
	NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Yang, 1996 — Quality rating (Efficacy, Safety): Fair-Poor, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: Taiwan

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 18	5	/ 0	/ 13

Inclusion criteria:
Adult patients whit moderate to severe chronic irreversible airway obstruction, who had been stable for at least 3 weeks.

Exclusion criteria:
Patients were excluded if they had diabetes mellitus, cardiovascular problems, infection, arthritis or muscular disorders, or an O2 saturation (SaO2) less than 85% when breathing room air. Patients with atopy (determined by history and blood tests, inclu

Comments:

Population: **Mean age:** 66 years
Gender: 15.38% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2mg	NR	13	66 years	15.38% Female
Fenoterol 2mg	NR	13	66 years	15.38% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 2mg		Fenoterol 2mg	
13	0.93(0.43)	13	0.91(0.43)
13	1.10(0.43)	13	1.11(0.43)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

O2 saturation
QTc interval
VPC

NR

Adverse Events:

K+, plasma

Albuterol 2mg		Fenoterol 2mg	
13	3.44(0.5)	13	3.44(0.32)
13	3.55(0.43)	13	3.24(0.29)
	NR(NR)		NR(NR)

Albuterol 2mg vs Fenoterol 2mg, p value: <0.001

Evidence Table 8. Albuterol vs fenoterol - RCTs: efficacy and safety

Yang, 1996	Quality rating (Efficacy, Safety): Fair-Poor, Fair

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Anani, 1989 — Quality rating (Efficacy, Safety): Poor, Poor

Design:

Study design: RCT Open Crossover **Run-in :** NR **Setting:** Community practice
Country: UK

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	30	6 /	0 /	24

Inclusion criteria:
Adults with chronic asthma

Exclusion criteria:
Patients who were unable to use a pressurized aerosol efficiently and those who had previously used the breath-actuated inhaler, Rotahaler.

Comments:

Population: **Mean age:** 35 years
Gender: 76.67% Female

Intervention:

Duration: 3 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug QID	400ug	30	35 years	76.67% Female
Terbutaline 500ug QID	500ug	30	35 years	76.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, evening before inhaler mean

Albuterol 400ug QID		Terbutaline 500ug QID	
30	NR(NR)	30	NR(NR)
24	378(NR)	24	386(NR)
	NR(NR)		NR(NR)

Albuterol 400ug QID vs Terbutaline 500ug QID, p value: 0.357

PEF, morning after inhaler mean

Albuterol 400ug QID		Terbutaline 500ug QID	
30	NR(NR)	30	NR(NR)
24	388(NR)	24	392(NR)
	NR(NR)		NR(NR)

Albuterol 400ug QID vs Terbutaline 500ug QID, p value: 0.541

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Anani, 1989 — Quality rating (Efficacy, Safety): Poor, Poor

PEF, morning before inhaler mean

Albuterol 400ug QID		Terbutaline 500ug QID	
30	NR(NR)	30	NR(NR)
24	332(NR)	24	348(NR)
	NR(NR)		NR(NR)

Albuterol 400ug QID vs Terbutaline 500ug QID, p value: 0.022

Effectiveness Outcomes:

Preference, effect

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Albuterol 400ug QID vs Terbutaline 500ug QID, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Palpitations

Albuterol 400ug QID		Terbutaline 500ug QID	
30	NR(NR)	30	NR(NR)
24	1(80)	24	1(80)
	NR(NR)		NR(NR)

Tremor

Albuterol 400ug QID		Terbutaline 500ug QID	
30	NR(NR)	30	NR(NR)
24	0(0)	24	1(80)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Capecchi, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Crossover **Run-in :** NR **Setting:** NR
Country: Italy

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	14	0	0	14

Inclusion criteria:
Patients who had suffered from bronchial asthma or chronic spastic bronchitis for several years with partially reversible airways obstruction and who presented with stable clinical conditions, independently of the degree of their bronchial obstruction.

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 50.2 years
Gender: 42.86% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.2mg	NR	14	50.2 years	42.86% Female
Terbutaline 0.5mg	NR	14	50.2 years	42.86% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.2mg		Terbutaline 0.5mg	
14	2.02(0.82)	14	1.98(0.75)
14	2.20(0.79)	14	2.17(0.79)
	NR(NR)		NR(NR)

FEV1

Albuterol 0.2mg		Terbutaline 0.5mg	
14	2.02(0.82)	14	1.98(0.75)
14	2.20(0.79)	14	2.16(0.79)
	NR(NR)		NR(NR)

Oxygen Saturation

Albuterol 0.2mg		Terbutaline 0.5mg	
14	95.5(2.24)	14	95.7(1.12)
14	95.2(5.24)	14	96.7(1.5)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Capecchi, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

PaCO2

Albuterol 0.2mg		Terbutaline 0.5mg	
14	36.2(3.74)	14	36.7(3.74)
14	35.0(3.37)	14	33.0(5.24)
	NR(NR)		NR(NR)

PaO2

Albuterol 0.2mg		Terbutaline 0.5mg	
14	77.9(9.73)	14	77.2(8.61)
14	78.8(16.09)	14	84.4(13.1)
	NR(NR)		NR(NR)

FEV1

Albuterol 0.2mg		Terbutaline 0.5mg	
14	2.02(0.82)	14	1.98(0.75)
14	2.11(0.82)	14	2.17(0.79)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

DBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	88.60(20.2)	14	87.50(22.82)
14	87.50(13.47)	14	90.70(17.21)
	NR(NR)		NR(NR)

SBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	149.60(35.55)	14	148.60(37.79)
14	147.90(30.68)	14	146.40(26.57)
	NR(NR)		NR(NR)

DBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	88.60(20.2)	14	87.50(22.82)
14	91.80(20.58)	14	88.20(21.33)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Capecchi, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

SBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	149.60(35.55)	14	148.60(37.79)
14	148.20(35.92)	14	146.80(35.92)
	NR(NR)		NR(NR)

DBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	88.60(20.2)	14	87.50(22.82)
14	83.20(20.58)	14	85.40(20.95)
	NR(NR)		NR(NR)

SBP

Albuterol 0.2mg		Terbutaline 0.5mg	
14	149.60(35.55)	14	148.60(37.79)
14	141.10(35.92)	14	148.60(33.67)
	NR(NR)		NR(NR)

Pulse rate

Albuterol 0.2mg		Terbutaline 0.5mg	
14	82.80(12.35)	14	86.00(11.97)
14	83.10(13.84)	14	80.40(10.85)
	NR(NR)		NR(NR)

Pulse rate

Albuterol 0.2mg		Terbutaline 0.5mg	
14	82.80(12.35)	14	86.00(11.97)
14	85.60(11.97)	14	87.60(13.1)
	NR(NR)		NR(NR)

Pulse rate

Albuterol 0.2mg		Terbutaline 0.5mg	
14	82.80(12.35)	14	86.00(11.97)
14	84.20(9.35)	14	85.30(11.6)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Capecchi, 1978 **Quality rating (Efficacy, Safety): Fair, Fair**

pH

Albuterol 0.2mg		Terbutaline 0.5mg	
14	7.45(0.03)	14	7.43(0.03)
14	7.47(0.04)	14	7.45(0.03)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

No side-effects of particular significance were observed.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Chandra, 2004 — Quality rating (Efficacy, Safety): Good, Good

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Community practice
Country: India

Sample:

# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
NR	/ NR	/ 60	NR	/ NR	/ 60

Inclusion criteria:

PEFR had to be more than 60-80% of the values predicted for the height; cooperative enough to perform spirometry; present with clinical features of mild (presence of coughing and wheezing without any formm of distress, cyanosis, increased respiratory rat

Exclusion criteria:

present with features of severe acute exacerbation or a lower respiratory tract infection; received a bronchodilator within the last 4 hours or presentation

Comments:

Population: **Mean age:** 9.5 years
Gender: 21.67% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	NR	29	9 years	20.69% Female
Terbutaline 250ug	NR	31	10 years	22.58% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1/FVC, median

Albuterol 100ug		Terbutaline 250ug	
29	0.92(NR)	31	1(NR)
29	0.98(NR)	31	1(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.445

PEFR, median % of predicted rate

Albuterol 100ug		Terbutaline 250ug	
29	57(NR)	31	63(NR)
29	84(NR)	31	86(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.723

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Chandra, 2004 **Quality rating (Efficacy, Safety): Good, Good**

FVC, median % predicted

Albuterol 100ug		Terbutaline 250ug	
29	53(NR)	31	49(NR)
29	63(NR)	31	55(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.54

FEV1, median % predicted

Albuterol 100ug		Terbutaline 250ug	
29	52(NR)	31	54(NR)
29	63(NR)	31	60(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.66

Effectiveness Outcomes:

Wheeze score: 1

Albuterol 100ug		Terbutaline 250ug	
29	15(52)	31	16(52)
29	8(28)	31	7(23)
	NR(NR)		NR(NR)

Wheeze score: 0

Albuterol 100ug		Terbutaline 250ug	
29	14(48)	31	15(48)
29	21(72)	31	24(77)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.66

Respiratory rate

Albuterol 100ug		Terbutaline 250ug	
29	26(NR)	31	26(NR)
29	26(NR)	31	26(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.72

Composite Asthma Score (CAS), median

Albuterol 100ug		Terbutaline 250ug	
29	1(NR)	31	2(NR)
29	1(NR)	31	1(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.750

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Chandra, 2004 — Quality rating (Efficacy, Safety): Good, Good

Adverse Events:

Heart rate

Albuterol 100ug		Terbutaline 250ug	
29	96(NR)	31	90(NR)
29	102(NR)	31	98(NR)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.8

Palpatations

Albuterol 100ug		Terbutaline 250ug	
29	NR(NR)	31	NR(NR)
29	1(3)	31	2(6)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: >0.05

Accessory muscle score: 1

Albuterol 100ug		Terbutaline 250ug	
29	6(21)	31	3(10)
29	3(10)	31	2(6)
	NR(NR)		NR(NR)

Accessory muscle score: 0

Albuterol 100ug		Terbutaline 250ug	
29	23(79)	31	28(90)
29	26(90)	31	29(94)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: 0.59

Tremor

Albuterol 100ug		Terbutaline 250ug	
29	NR(NR)	31	NR(NR)
29	4(14)	31	3(10)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: >0.05

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Choo-Kang, 1973 — Quality rating (Efficacy, Safety): Poor, Poor

Design:

Study design: RCT NR Crossover **Run-in :** NR **Setting:** Community practice
Country: Scotland

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	21	0	8	13

Inclusion criteria:
Chronic asthma and known response to salbutamol by inhalation

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 49.3 years
Gender: NR% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	13	49.3 years	NR
Terbutaline 500ug	NR	13	49.3 years	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Salbutamol 200ug		Terbutaline 500ug	
13	NR(NR)	13	NR(NR)
13	NR(NR)	13	NR(NR)
	0.52(0.4)		0.50(0.27)

Salbutamol 200 ug vs Terbutaline 500ug, p value: 0.3

FEV1, mean change

Salbutamol 200ug		Terbutaline 500ug	
13	NR(NR)	13	NR(NR)
13	NR(NR)	13	NR(NR)
	0.56(0.32)		0.44(0.28)

Salbutamol 200ug vs Terbutaline 500ug, p value: 0.1

FEV1, mean change

Salbutamol 200ug		Terbutaline 500ug	
13	NR(NR)	13	NR(NR)
13	NR(NR)	13	NR(NR)
	0.44(0.31)		0.36(0.30)

Salbutamol 200ug vs Terbutaline 500ug, p value: <0.2

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Choo-Kang, 1973 — Quality rating (Efficacy, Safety): Poor, Poor

FEV1, mean change

Salbutamol 200 ug		Terbutaline 500ug	
13	NR(NR)	13	NR(NR)
13	NR(NR)	13	NR(NR)
	0.26(0.28)		0.29(0.28)

Salbutamol 200ug vs Terbutaline 500ug, p value: 0.8

FEV1, maximal

Albuterol 200ug		Terbutaline 500ug	
13	NR(NR)	13	NR(NR)
13	NR(NR)	13	NR(NR)
	0.68(0.37)		0.60(0.27)

Albuterol 200ug vs Terbutaline 500ug, p value: <0.15

Other Efficacy/Effectiveness Outcomes and Comments:

FVC changes were similar, and are not reported in further detail. There was a slight fall in heart rate and both diastolic and systolic blood pressures after inhalations, changes not reported in any further detail.

Graph displays changes in FEV1 at time intervals up to seven hours after inhalation.

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Eryonucu, 2001 — Quality rating (Efficacy, Safety): NA, Good

Design:

Study design: RCT NR Crossover **Run-in :** **Setting:** NR

Country: Turkey

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	20	0 /	0 /	20

Inclusion criteria:

Adults newly diagnosed or known cases of bronchial asthma (American Thoracic Society guidelines); had not received oral or inhaled asthma medication (B2-agonists and corticosteroids) for the previous 2 months; shouwed mild to moderate decrease in forced e

Exclusion criteria:

Patients with diabetes mellitus, renal disorders or any diseases that might have influenced the autonomic function

Comments:

Population: **Mean age:** 37 years

Gender: 55% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	20	37 years	55% Female
Terbutaline 500ug	NR	20	37 years	55% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

Total power
Low frequent power (LF)
High frequent power (HF)
LF/HF
Heart rate variability (HRV)

NR

Adverse Events:

Heart rate

Albuterol 200ug		Terbutaline 500ug	
20	74(4)	20	74(3)
20	85(4)	20	85(4)
	NR(NR)		NR(NR)

Heart rate

Albuterol 200ug		Terbutaline 500ug	
20	74(4)	20	74(3)
20	78(5)	20	77(3)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Eryonucu, 2001 **Quality rating (Efficacy, Safety): NA, Good**

Heart rate

Albuterol 200ug		Terbutaline 500ug	
20	74(4)	20	74(3)
20	81(3)	20	79(3)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Francis, 1983 **Quality rating (Efficacy, Safety): Fair, NA**

Design:

Study design: RCT NR Crossover **Run-in :** NR **Setting:** Community practice
Country: Australia

Sample:

# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
NR /	NR /	10	0 /	0 /	10

Inclusion criteria:
Stable outpatient asthmatic children

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 12 years
Gender: 30% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	10	12 years	30% Female
Terbutaline 500ug	NR	10	12 years	30% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 400ug		Terbutaline 500ug	
10	1.81(NR)	10	1.81(NR)
10	NR(NR)	10	NR(NR)
	0.56(0.25)		0.26(0.19)

Albuterol 400ug vs Terbutaline 500ug, p value: <0.01

FEV1

Albuterol 400ug		Terbutaline 500ug	
10	1.81(NR)	10	1.81(NR)
10	NR(NR)	10	NR(NR)
	0.46(0.19)		0.23(0.16)

Albuterol 400ug vs Terbutaline 500ug, p value: <0.01

Other Efficacy/Effectiveness Outcomes and Comments:

Maximum mid-expiratory flow (MMEF)

NR

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Gioulekas, 1996 — Quality rating (Efficacy, Safety): Poor, Poor

Design:

Study design: RCT Open Crossover **Run-in :** NR **Setting:** Community practice
Country: Greece

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 32	7	/ NR	/ 25

Inclusion criteria:

a reversibility of at least 15% in FEV1 or PEF after 3 x 0.5 mg doses of terbutaline via Turbuhaler, and the patients had to be sufficiently stable not to have experienced a marked exacerbation of their asthma during the month prior to the study.

Exclusion criteria:

hypersensitivity to terbutaline or salbutamol; significant concomitant disease of any system; current respiratory infection; previous use of Rotahaler

Comments:

Population: **Mean age:** 34 years
Gender: 34.38% Female

Intervention:

Duration: 3 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.4mg TID	1.2 mg	32	34 years	34.38% Female
Terbutaline 0.5mg TID	1.5 mg	32	34 years	34.38% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, evening mean

Albuterol 0.4mg TID	Terbutaline 0.5mg TID
32 408.1(NR)	32 408.1(NR)
25 428(125)	25 446(130)
NR(NR)	NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: 0.008

PEF, morning mean

Albuterol 0.4mg TID	Terbutaline 0.5mg TID
32 408.1(NR)	32 408.1(NR)
25 410(117)	25 426(117)
NR(NR)	NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: 0.016

Effectiveness Outcomes:

No. of rescue treatment required

Albuterol 0.4mg TID
32 NR(NR)
25 8(32)
NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Gioulekas, 1996 **Quality rating (Efficacy, Safety): Poor, Poor**

	Terbutaline 0.5mg TID
32	NR(NR)
25	9(36)
	NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: >0.05

Preference, overall

Albuterol 0.4mg TID		Terbutaline 0.5mg TID		No preference	
32	NR(NR)	32	NR(NR)	32	NR(NR)
25	4(16)	25	11(56)	25	10(40)
	NR(NR)		NR(NR)		NR(NR)

Preference, effect

Albuterol 0.4mg TID		Terbutaline 0.5mg TID		No preference	
32	NR(NR)	32	NR(NR)	32	NR(NR)
25	8 8(32)	25	13(52)	25	4(16)
	NR(NR)		NR(NR)		NR(NR)

Symptom scores from diary recording, nighttime

Albuterol 0.4mg TID		Terbutaline 0.5mg TID	
32	NR(NR)	32	NR(NR)
25	0.65(NR)	25	0.52(NR)
	NR(NR)		NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: >0.05

Symptom scores from diary recording, daytime

Albuterol 0.4mg TID		Terbutaline 0.5mg TID	
32	NR(NR)	32	NR(NR)
25	0.55(NR)	25	0.4(NR)
	NR(NR)		NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: >0.05

Preference, side effect

Albuterol 0.4mg TID		Terbutaline 0.5mg TID		No preference	
32	NR(NR)	32	NR(NR)	32	NR(NR)
25	1(4)	25	10(10)	25	14(56)
	NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Gioulekas, 1996 **Quality rating (Efficacy, Safety): Poor, Poor**

Other Adverse Events and Comments:

Two pts, allocated to terbutaline-albuterol, discontinued the study during terbutaline treatment: one due to tachycardia, exhaustion & tremor & one due to respiratory infection. Five pts allocated to albuterol-terbutaline were lost to follow-up during salbutamol treatment.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Hung, 2001 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Parallel **Run-in :** NR **Setting:** Emergency
Country: Taiwan

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 30	NR	/ NR	/ 30

Inclusion criteria:
Acute asthma

Exclusion criteria:
received treatment by beta2-adrenergic agonist within 3 days

Comments:

Population: **Mean age:** 8.18 years
Gender: 43.33% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.125mg/kg	NR	15	8.34 years	40% Female
Terbutaline 0.125mg/kg	NR	15	8.02 years	46.67% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

SvO2

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	58.15(9.62)	30	74.21(11.74)
30	79.41(13.89)	30	80.81(13.52)
	NR(NR)		NR(NR)

PvCO2

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	41.48(3.44)	30	36.20(7.14)
30	33.23(3.52)	30	34.33(6.81)
	NR(NR)		NR(NR)

PvO2

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	34.12(4.50)	30	43.60(5.67)
30	60.13(3.56)	30	47.41(6.73)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Hung, 2001 — Quality rating (Efficacy, Safety): Fair, Fair

PEFR

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	119.41(48.52)	30	128.56(56.12)
30	168.70(74.59)	30	156.78(59.64)
	NR(NR)		NR(NR)

Effectiveness Outcomes:

Respiratory rate

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	35.34(3.50)	30	30.20(5.12)
30	27.41(2.85)	30	26.1(3.25)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	131.58(8.53)	30	123.50(7.72)
30	132.75(9.32)	30	121.50(8.13)
	NR(NR)		NR(NR)

K+, serum level

Albuterol 0.125mg/kg		Terbutaline 0.125mg/kg	
30	3.74(0.51)	30	3.69(0.52)
30	3.12(0.85)	30	3.22(0.48)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Lindsay, 1994 — Quality rating (Efficacy, Safety): Poor, Fair

Design:

Study design: RCT Open Crossover **Run-in :** 2 weeks days **Setting:** Community practice
Country: Australia

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 46	1	/ NR	/ 45

Inclusion criteria:

Adults and children (>=7 yrs) with previously diagnosed and currently stable asthma as defined: no office visits for asthma exacerbation, no emergency room visits or hospitalizations due to asthma, or use of antibiotics for asthma or respiratory illness i

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 34.5 years
Gender: 45.65% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.1mg BID	0.2mg	46	34.5 years	45.65% Female
Terbutaline 0.5mg BID	1.0mg	46	34.5 years	45.65% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

Diurnal variability over the last 14 days

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	18(6.71)	45	18(6.71)
45	18(6.71)	45	17(6.71)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.2

FVC, over the last 14 days

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	NR(NR)	45	NR(NR)
45	85(20.12)	45	84(20.12)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.3

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Lindsay, 1994 — Quality rating (Efficacy, Safety): Poor, Fair

FEV1, over the last 14 days

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	NR(NR)	45	NR(NR)
45	72(26.83)	45	71(26.83)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.3

PEF, change in pred over the last 14 days

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	NR(NR)	45	NR(NR)
45	NR(NR)	45	NR(NR)
	11(6.71)		11(13.42)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.3

PEF, morning over the last 14 days

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	79(20.12)	45	79(20.12)
45	90(20.12)	45	89(20.12)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.6

Effectiveness Outcomes:

No. of doses taken over 24hrs

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	NR(NR)	45	NR(NR)
45	5.8(2.3)	45	3.2(1.6)
	NR(NR)		NR(NR)

Total symptom score

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	2.0(2.01)	45	1.8(2.01)
45	2.0(2.01)	45	1.8(2.01)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.3

Breathlessness on exertion, symptom score

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	0.6(0.67)	45	0.6(0.67)
45	0.6(2.68)	45	0.6(0.67)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.9

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Lindsay, 1994 — Quality rating (Efficacy, Safety): Poor, Fair

Wheeze, symptom score

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	0.5(0.67)	45	0.4(0.67)
45	0.5(0.67)	45	0.5(0.67)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.4

Asthma, excerbations

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	NR(NR)	45	NR(NR)
45	2(4)	45	1(2)
	NR(NR)		NR(NR)

Preference

Albuterol 0.1mg BID		Terbutaline 0.5mg BID		No preference	
46	NR(NR)	46	NR(NR)	46	NR(NR)
46	18(39)	46	20(44)	46	8(17)
	NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Data reported over the last 14 days of each treatment.

Adverse Events:

Sleep distrubance, symptom score

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	0.4(0.67)	45	0.4(0.67)
45	0.3(0.67)	45	0.3(0.67)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.5

Cough, symptom score

Albuterol 0.1mg BID		Terbutaline 0.5mg BID	
45	0.4(0.67)	45	0.3(0.67)
45	0.3(0.67)	45	0.3(0.67)
	NR(NR)		NR(NR)

Albuterol 0.1mg BID vs Terbutaline 0.5mg BID, p value: 0.06

Other Adverse Events and Comments:

No differences detected in occurrence of AEs btwn treatments; 30% pts reported AEs during 2wk run-in. 51% pts reported Aes when taking terb, 54% pts reported AEs when taking alb. AEs: aggravated asthma & upper respiratory tract infection

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Lopes dos Santos, 1991 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice
Country: Portugal & Sweden

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	19	0 /	0 /	19

Inclusion criteria:
Children known to have exercise-induced asthma; not taking oral B2-agonists or theophyllines

Exclusion criteria:
Diabetes mellitus; significant cardiac disease; hypersensitivity to sympathomimetics; concomitant treatment with sodium cromoglycate

Comments:

Population: **Mean age:** 10 years
Gender: 26.32% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.4mg	NR	19	10 years	26.32% Female
Terbutaline 0.5mg	NR	19	10 years	26.32% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

PEF: no significant differences between treatment, data NR.
Bronchoconstriction: none
Extra medication neede: none

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Malinen, 2000 — Quality rating (Efficacy, Safety): Good, Good

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Finland

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 29	0	/ 0	/ 29

Inclusion criteria:

Diagnosed asthma; show an improvement in forced expiratory volume in 1 second (FEV1), or peak expiratory flow (PEF) values of at least 15% after inhaling 200 ug of salbutamol, or 500 ug of terbutaline within 4 weeks prior to entering the study; no asthma

Exclusion criteria:

No previous experience of the inhalers in the study.

Comments:

Population: **Mean age:** 48 years

Gender: 55.17% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	NR	29	48 years	55.17% Female
Terbutaline 250ug	NR	29	48 years	55.17% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, AUC after treatment

Albuterol 100ug		Terbutaline 250ug	
29	NR(NR)	29	NR(NR)
29	715(296)	29	704(267)
	NR(NR)		NR(NR)

FEV1, maximum % change

Albuterol 100ug		Terbutaline 250ug	
29	NR(NR)	29	NR(NR)
29	NR(NR)	29	NR(NR)
	12.7(12.4)		13.1(10.8)

FEV1, after treatment

Albuterol 100ug		Terbutaline 250ug	
29	2.81(1.18)	29	2.74(1.07)
29	3.14(1.26)	29	3.07(1.11)
	NR(NR)		NR(NR)

Albuterol 100ug vs Terbutaline 250ug, p value: NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Malinen, 2000 **Quality rating (Efficacy, Safety): Good, Good**

Other Efficacy/Effectiveness Outcomes and Comments:

Delivery device acceptability

NR

Adverse Events:

No. of patients reported adverse events

Albuterol 100ug		Terbutaline 250ug	
29	NR(NR)	29	NR(NR)
29	4(14)	29	5(17)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

Headache: alb 1, terb 1. Other: terb: 2 cough & 1 bronchospasm.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: Romania

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	63	0 /	0 /	63

Inclusion criteria:
Chronic bronchitis (CIBA Guest Symposium and American Thoriacic Society criteria); a response of the FEV1 of at least 10% of baseline values 30 minutes after inhalation of 1500 ug orciprenaline aerosol

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 56.5 years
Gender: 25.4% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	63	56.5 years	25.4% Female
Terbutaline 500ug	NR	63	56.5 years	25.4% Female
Fenoterol 400ug	NR	63	56.5 years	25.4% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	0.325(NR)		0.305(NR)		0.285(NR)

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Effectiveness Outcomes:

Preference

Albuterol 400ug		Terbutaline 500ug		Fenoterol 400ug		No preference	
63	NR(NR)	63	NR(NR)	63	NR(NR)	63	NR(NR)
63	19(30.2)	63	16(25.4)	63	21(33.3)	63	7(11.1)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

VC

NR

Other Adverse Events and Comments:

No significant changes in HR.
No significant changes in BP.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Munzenberger, 1989 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT NR Crossover **Run-in :** NR **Setting:** Community practice

Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	20	NR /	NR /	20

Inclusion criteria:

Diagnosed asthma; previous demonstration of bronchodilator responsiveness with at least 15% increase from baseline in FEV1 following the inhalation of a beta agonist from a metered-dose inhaler.

Exclusion criteria:

Taking steroids or a known sensitivity to either study drug

Comments:

Population: **Mean age:** 17.8 years

Gender: 35% Female

Intervention:

Duration: 2 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	20	17.8 years	35% Female
Terbutaline 360ug	NR	20	17.8 years	35% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV25 75, mean % predicted

<0.05		Terbutaline 360ug	
20	47.5(28.5)	20	42.9(29.0)
20	69.6(NR)	20	64.0(NR)
	NR(NR)		NR(NR)

FEV1, mean % predicted

Albuterol 400ug		Terbutaline 360ug	
20	74.3(18)	20	71.3(19.1)
20	88.3(NR)	20	87.3(NR)
	NR(NR)		NR(NR)

Notes: Significant mean percent increases from the baseline at all post-dose values for both drugs (p <0.05)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Munzenberger, 1989 **Quality rating (Efficacy, Safety): Fair, Poor**

FEV25 75, mean % predicted

Albuterol 400ug		Terbutaline 360ug	
20	47.5(28.5)	20	42.9(29.0)
20	73.8(NR)	20	66.6(NR)
	NR(NR)		NR(NR)

Notes: No significant difference between drugs.

FEV1, mean % predicted

Albuterol 400ug		Terbutaline 360ug	
20	74.3(18)	20	71.3(19.1)
20	93.6(NR)	20	90.1(NR)
	NR(NR)		NR(NR)

Notes: Significant mean percent increases from the baseline at all post-dose values for both drugs (p <0.05)

FEV1, mean % predicted, maximum

Albuterol 400ug		Terbutaline 360ug	
20	74.3(18)	20	71.3(19.1)
20	96.6(NR)	20	91.5(NR)
	NR(NR)		NR(NR)

Albuterol 400ug vs Terbutaline 360ug, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

Significant mean percent increases from the baseline at all post-dose values for both drugs (p <0.05) for FEV1.

Adverse Events:

Total adverse events

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	16(80)	20	13(65)
	NR(NR)		NR(NR)

Heart rate, mean peak increase

Albuterol 400ug		Terbutaline 360ug	
20	78.8(12.5)	20	75.4(8.6)
20	83.6(NR)	20	78.2(NR)
	4.8(NR)		2.8(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Munzenberger, 1989 **Quality rating (Efficacy, Safety): Fair, Poor**

Palpitations

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	3(15)	20	1(5)
	NR(NR)		NR(NR)

Nausea

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	2(10)	20	1(5)
	NR(NR)		NR(NR)

Vomiting

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	0(0)	20	1(5)
	NR(NR)		NR(NR)

Bad taste

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	1(5)	20	2(10)
	NR(NR)		NR(NR)

Headache

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	4(20)	20	3(15)
	NR(NR)		NR(NR)

Nervousness

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	1(5)	20	2(10)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Munzenberger, 1989 **Quality rating (Efficacy, Safety): Fair, Poor**

Vertigo

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	2(10)	20	1(5)
	NR(NR)		NR(NR)

Insomnia

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	0(0)	20	1(5)
	NR(NR)		NR(NR)

Tremor

Albuterol 400ug		Terbutaline 360ug	
20	NR(NR)	20	NR(NR)
20	3(15)	20	1(5)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

No significant change in PR, systolic or diastolic BP at any time point. 10 pts reported side effects w/ one accounting for 15 of 29 reported AEs. NSD between the drugs for any side effect.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Oldaeus, 1995 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT Open Crossover **Run-in :** 7 days days **Setting:** Community practice
Country: Sweden

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	20	0 /	0 /	20

Inclusion criteria:

Reversible airway obstruction defined as at least 15% improvement in peak expiratory flow rate 15 minutes after inhalation of 0.5 mg terbutaline and to be in need of bronchodilator therapy

Exclusion criteria:

Cardiac disease, thyrotoxicosis, hypersensitivity to sympathomimetics, ongoing seasonal allergy, or respiratory tract infection; no oral steroids

Comments:

Population: **Mean age:** 3.5 years
Gender: 70% Female

Intervention:

Duration: 2 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.4mg TID	1.2mg	20	3.5 years	70% Female
Terbutaline 0.5mg TID	1.5mg	20	3.5 years	70% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEF, evening

Albuterol 0.4mg TID	Terbutaline 0.5mg TID
20 130(43)	20 133(46)
20 164(33)	20 158(46)
NR(NR)	NR(NR)

PEF, morning

Albuterol 0.4mg TID	Terbutaline 0.5mg TID
20 116(37)	20 118(39)
20 149(40)	20 150(43)
NR(NR)	NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: >0.05

Effectiveness Outcomes:

Extra inhalations, night

Albuterol 0.4mg TID

20 NR(NR)
20 0.10(0.20)
NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Oldaeus, 1995	Quality rating (Efficacy, Safety): Fair, Fair

	Terbutaline 0.5mg TID
20	NR(NR)
20	0.13(0.31)
	NR(NR)

Extra inhalations, day

Albuterol 0.4mg TID	
20	NR(NR)
20	0.11(.29)
	NR(NR)

Terbutaline 0.5mg TID	
20	NR(NR)
20	0.13(0.21)
	NR(NR)

Preference

Albuterol 0.4mg TID	
20	NR(NR)
20	12(60)
	NR(NR)

Terbutaline 0.5mg TID	
20	NR(NR)
20	5(25)
	NR(NR)

No preference	
20	NR(NR)
20	1(5)
	NR(NR)

Neither	
20	NR(NR)
20	1(5)
	NR(NR)

Albuterol 0.4mg TID vs Terbutaline 0.5mg TID, p value: 0.14

Asthma, symptom score night

Albuterol 0.4mg TID	
20	NR(NR)
20	0.47(0.6)
	NR(NR)

Terbutaline 0.5mg TID	
20	NR(NR)
20	0.46(0.58)
	NR(NR)

Asthma, symptom score day

Albuterol 0.4mg TID	
20	NR(NR)
20	0.11(0.29)
	NR(NR)

Terbutaline 0.5mg TID	
20	NR(NR)
20	0.38(0.46)
	NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Adverse events (score 0-3), night

Albuterol 0.4mg TID	
20	NR(NR)
20	0.05(0.22)
	NR(NR)

Terbutaline 0.5mg TID	
20	NR(NR)
20	0.05(0.22)
	NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Oldaeus, 1995 — Quality rating (Efficacy, Safety): Fair, Fair

Adverse events (score 0-3), day

Albuterol 0.4mg TID		Terbutaline 0.5mg TID	
20	NR(NR)	20	NR(NR)
20	0.15(0.49)	20	0.09(0.28)
	NR(NR)		NR(NR)

Restlessness

Albuterol 0.4mg TID		Terbutaline 0.5mg TID	
20	NR(NR)	20	NR(NR)
20	3(15)	20	3(15)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Pedersen, 1985 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: Denmark

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	24	0 /	0 /	24

Inclusion criteria:

The child should participate on 3 different study days, and the variation in FEV1 before exercise and variation in pretreatment FEV1 during all 3 tests days had to be less than 15%. If a child was treated on more than three occasions the results from the

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 9.6 years
Gender: 33.33% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.2mg	NR	24	9.6 years	33.33% Female
Terbutaline 0.25mg	NR	24	9.6 years	33.33% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean increase after the second treatment

Albuterol 0.2mg		Terbutaline 0.25mg	
25	NR(NR)	25	NR(NR)
25	NR(NR)	25	NR(NR)
	0.28(NR)		0.23(NR)

Albuterol 0.2mg vs Terbutaline 0.25mg, p value: >0.05

FEV1, mean increase after the first treatment

Albuterol 0.2mg		Terbutaline 0.25mg	
25	NR(NR)	25	NR(NR)
25	NR(NR)	25	NR(NR)
	0.43(NR)		0.29(NR)

Albuterol 0.2mg vs Terbutaline 0.25mg, p value: <0.01

Effectiveness Outcomes:

Aminophylline required after treatment

Albuterol 0.2mg		Terbutaline 0.25mg	
24	NR(NR)	24	NR(NR)
24	5(21)	24	2(8)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Pedersen, 1985 **Quality rating (Efficacy, Safety): Fair, NA**

Other Efficacy/Effectiveness Outcomes and Comments:

FEV1, 5 mins and 10 mins after the first treatment:
- albuterol < terbutaline, p<0.05
Breathholding periods;
- varied from 5 to 10 sec (mean 8.7 sec), no significant difference between treatment.

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Parallel **Run-in :** **Setting:** NR
Country: Brazil

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	21	NR	NR	21

Inclusion criteria:
Children presenting with acute bronchial asthma and demonstrated an FEV1 lower than 80% of nromal predicted value.

Exclusion criteria:
Children should not have taken long-acting theophylline, antihistamines, or corticosteroids for 24 hr and beta-adrenergic agents or other bronchodilator medication for 12 hr before the study.

Comments:

Population: **Mean age:** 10.41 years
Gender: 42.86% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 5mg	NR	11	NR	NR
Fenoterol 0.083mg/kg	NR	14	NR	NR
Terbutaline 0.1mg/kg	NR	12	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 1.04(0.53)	21 1.18(0.50)	21 0.94(0.44)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 Quality rating (Efficacy, Safety): Fair, Fair

FEV1, mean % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Bronchodilator effect, mean duration

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg			
21	NR(NR)	21	NR(NR)	21	NR(NR)	21	NR(NR)
21	365(NR)	21	287(NR)	21	NR(NR)	21	285(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Figures interpolated from graph in text.

Adverse Events:

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.
3/11 (27%) of albuterol patients had larger HR increases (36, 60 and 70 bpm respectively); 2/14 (14%) of fenoterol patients had larger heart r increases (38 & 60 bpm)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 **Quality rating (Efficacy, Safety): Fair, Fair**

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
93(NR)	86(NR)	104(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
106(NR)	34(NR)	90(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
151(NR)	93(NR)	62(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
175(NR)	167(NR)	119(NR)

Notes: Figures interpolated from graph in text.

Other Adverse Events and Comments:

NR

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Towns, 1983 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Community practice

Country: Australia

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	25	0 /	0 /	25

Inclusion criteria:

Children with stable moderate to severe asthma.

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 9 years

Gender: 48% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	25	9 years	48% Female
Terbutaline 500ug	NR	25	9 years	48% Female

Outcomes:

Reporting of data is as follows:

Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, % control

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: NR

Notes: Data not reported, estimated from the graph.

PEFR, % control

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: <0.05

Notes: Data not reported, estimated from the graph.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Towns, 1983 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, % control

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: <0.02

Notes: Data not reported, estimated from the graph.

PEFR, % control

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: <0.05

Notes: Data not reported, estimated from the graph.

FEV1, % control

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
24	NR(NR)	24	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: <0.05

Notes: Data not reported, estimated from the graph.

Effectiveness Outcomes:

Preference

Albuterol 200ug		Terbutaline 500ug		No preference	
25	NR(NR)	25	NR(NR)	25	NR(NR)
25	18(72)	25	5(20)	25	2(8)
	NR(NR)		NR(NR)		NR(NR)

Symptom score

Albuterol 200ug		Terbutaline 500ug	
25	NR(NR)	25	NR(NR)
25	NR(NR)	25	NR(NR)
	NR(NR)		NR(NR)

Albuterol 200ug vs Terbutaline 500ug, p value: >0.05

Other Efficacy/Effectiveness Outcomes and Comments:

VC

NR

Other Adverse Events and Comments:

No significant change in HR, respiratory rate or cough (no data reported).

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Vilsvik, 1991 — Quality rating (Efficacy, Safety): Poor, Poor

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: Norway

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	21	21	1	5	16

Inclusion criteria:

Patients with exercise-induced asthma were included if they, in a pretrial test, showed a post-exercise fall in peak expiratory flow rate (PEFR) of at least 20%

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 30.6 years

Gender: NR% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.1mg	NR	16	30.6 years	43.75% Female
Terbutaline 0.5mg	NR	16	30.6 years	43.75% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR, second dose

Albuterol 0.1mg		Terbutaline 0.5mg	
21	300(78)	21	301(67)
21	470(94)	21	441(91)
	170(NR)		140(NR)

Albuterol 0.1mg vs Terbutaline 0.5mg, p value: 0.07

PEFR, first dose

Albuterol 0.1mg		Terbutaline 0.5mg	
21	300(78)	21	301(67)
21	445(95)	21	399(98)
	145(NR)		98(NR)

Albuterol 0.1mg vs Terbutaline 0.5mg, p value: 0.02

PEFR

Albuterol 0.1mg		Terbutaline 0.5mg	
16	450(91)	16	443(90)
16	422(94)	16	417(79)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Vilsvik, 1991	Quality rating (Efficacy, Safety): Poor, Poor

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

The PR did not differ during the study days. No AEs were registered for any of the pts on any of the study drug.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Vilsvik, 1993 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT Open Crossover **Run-in :** 1-2 weeks days **Setting:** NR

Country: Norway

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	159	11 /	1 /	158

Inclusion criteria:

Outpatients aged 18 years or over suffering from reversible airway disease and had a regular requirement for inhaled B2-agonist at least 2 times a day, either alone or in addition to other therapy. They were required to have a basal FEV1 of at least 1 L

Exclusion criteria:

Patients treated with anitbiotics because of respiratory infections within the last 4 weeks

Comments:

Population: **Mean age:** 49 years

Gender: 39.62% Female

Intervention:

Duration: 2 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.1mg	0.2mg	159	49 years	39.62% Female
Terbutaline 0.5mg	NR	159	49 years	39.62% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

PEFR, evening mean

Albuterol 0.1mgX2		Terbutaline 0.5mg	
158	384(NR)	158	392(NR)
158	439(NR)	158	437(NR)
	NR(NR)		NR(NR)

Albuterol 0.1mgX2 vs Terbutaline 0.5mg, p value: NS

Notes: Before inhalation, there was a difference 7.0 +/- 26.4 L/min in favor of Terbutaline, p<0.01

PEFR, morning mean

Albuterol 0.1mgX2		Terbutaline 0.5mg	
158	354(NR)	158	362(NR)
158	418(NR)	158	412(NR)
	NR(NR)		NR(NR)

Albuterol 0.1mgX2 vs Terbutaline 0.5mg, p value: 0.01

Notes: Before inhalation, there was a difference 8.2 +/- 29.1 L/min in favor of Terbutaline, p<0.01

Effectiveness Outcomes:

Preference

Albuterol 0.1mgX2

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Vilsvik, 1993 **Quality rating (Efficacy, Safety): Fair, Fair**

159	NR(NR)	Terbutaline 0.5mg		No preference	
159	39(24.5)	159	NR(NR)	159	NR(NR)
	NR(NR)	159	87(54.7)	159	33(20.7)
			NR(NR)		NR(NR)

Albuterol 0.1mgX2 vs Terbutaline 0.5mg, p value: <0.001

Notes: 39% in favor of Terbutaline

Asthma, symptom score evening mean

Albuterol 0.1mgX2		Terbutaline 0.5mg	
158	NR(NR)	158	NR(NR)
158	0.57(NR)	158	0.50(NR)
	NR(NR)		NR(NR)

Albuterol 0.1mgX2 vs Terbutaline 0.5mg, p value: <0.05

Asthma, symptom score morning mean

Albuterol 0.2mg		Terbutaline 0.5mg	
156	NR(NR)	156	NR(NR)
156	0.77(NR)	156	0.67(NR)
	NR(NR)		NR(NR)

Albuterol 0.1mgX2 vs Terbutaline 0.5mg, p value: <0.001

Other Efficacy/Effectiveness Outcomes and Comments:

No rescue medication was used in either period

Adverse Events:

Irritation symptoms

Albuterol 0.1mgX2		Terbutaline 0.5mg	
159	NR(NR)	159	NR(NR)
159	44(27.6)	159	18(11.3)
	NR(NR)		NR(NR)

Notes: A difference of 16.5% in favor of terbutaline is statistically significant, P<0.001

Coordination problems

Albuterol 0.1mgX2		Terbutaline 0.5mg	
159	NR(NR)	159	NR(NR)
159	12(7.5)	159	4(2.5)
	NR(NR)		NR(NR)

Notes: A differenc of 5% in favor of terbutaline is statistically significant, p<0.05

Other Adverse Events and Comments:

Twenty three pts reported the same AEs; eight in the albuterol period & fourteen in both periods; all were mild or moderate & consisted mainly of tremors & palpitations. The difference of 9.4% is statistically significant in favor of albuterol, p<0.05.

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Webb, 1982 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 16	NR	/ NR	/ 16

Inclusion criteria:

Patients with at least 15% reversibility to an inhaled B2-sympathomimetic and who were not taking long-term oral or inhaled corticosteroids.

Exclusion criteria:

NR

Comments:

Population: **Mean age:** NR years

Gender: NR% Female

Intervention:

Duration: 1 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	NR	16	NR	NR
Terbutaline 500ug	NR	16	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 200ug		Terbutaline 500ug	
16	2.02(NR)	16	2.12(NR)
16	2.43(NR)	16	2.49(NR)
	NR(NR)		NR(NR)

FEV1

Albuterol 200ug		Terbutaline 500ug	
16	2.02(NR)	16	2.12(NR)
16	2.37(NR)	16	2.42(NR)
	NR(NR)		NR(NR)

FEV1

Albuterol 200ug		Terbutaline 500ug	
16	2.02(NR)	16	2.12(NR)
16	2.41(NR)	16	2.47(NR)
	NR(NR)		NR(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Webb, 1982 — Quality rating (Efficacy, Safety): Fair, Poor

FEV1

Albuterol 200ug		Terbutaline 500ug	
16	2.02(NR)	16	2.12(NR)
16	2.28(NR)	16	2.31(NR)
	NR(NR)		NR(NR)

Peak flow

Albuterol 200ug		Terbutaline 500ug	
16	NR(NR)	16	NR(NR)
16	305(NR)	16	305(NR)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

FVC
PEF
FEF25-75

NR

Other Adverse Events and Comments:

Palpitations were noted in 2 pts following aerosol turbutaline; lightheadedness in one patient after aerosol salbutamol

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 **Quality rating (Efficacy, Safety): Fair, Good**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: UK

Sample: # Screened / Eligible / Enrolled: NR / NR / 10 # Withdrawn / Lost to follow-up / Analyzed: NR / NR / 10

Inclusion criteria:
Asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** NR years
Gender: 20% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	2,600 ug	10	NR	20% Female
Fenoterol 200ug	5,200 ug	10	NR	20% Female
Terbutaline 250ug	6,500 ug	10	NR	20% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.63(NR)		0.76(NR)		0.63(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.98(NR)		1.05(NR)		1.10(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.87(NR)		1.10(NR)		0.92(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 **Quality rating (Efficacy, Safety): Fair, Good**

Other Efficacy/Effectiveness Outcomes and Comments:

Mean area under the curve - within subject differences for fenoterol vs albuterol(SE) and terbutaline(SE):
FEV1 - fenoterol 1.77; albuterol -0.16 (0.15); terbutaline -0.08 (0.15)
Potassium concentration - fenoterol -0.82; albuterol 0.54 (0.17); terbutaline 0.33(0.18)

All values interpolated from graphs in text

Adverse Events:

Heart rate, mean maximum change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	8(9)		29(24)		8(14)

Palpitations

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	1(10)	10	3(30)	10	3(30)
	NR(NR)		NR(NR)		NR(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.10(NR)		0.06(NR)		0.03(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.42(NR)		-0.73(NR)		-0.45(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.01(NR)		-0.42(NR)		-0.20(NR)

Evidence Table 9. Albuterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 **Quality rating (Efficacy, Safety): Fair, Good**

Headache

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	3(30)	10	5(50)	0	2(20)
	NR(NR)		NR(NR)		NR(NR)

Tremor

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	4(40)	10	6(60)	10	4(40)
	NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 10. Metaproterenol vs terbutaline - RCTs: efficacy and safety

Chester, 1978 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	16	0 /	0 /	16

Inclusion criteria:

Ambulatory subjects with reverisible obstructive airways diseases. Criteria fro entry inlcuded an elevation of specific airway resistance (Sraw) and a forced expiratory volume in one second (FEV1) less than 70% of each subject's predicted normal value. Re

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 36 years
Gender: 31.25% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Metaproterenol 1300ug	NR	16	36 years	31.25% Female
Terbutaline 500ug	NR	16	36 years	31.25% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV50

NR NR(NR)
NR NR(NR)
NR(NR)

FEV25-75

Metaproterenol 1300ug	Terbutaline 500ug
16 NR(NR)	16 NR(NR)
16 NR(NR)	16 NR(NR)
NR(NR)	NR(NR)

Notes: Terbutaline reached maximum effect at 2 hrs. Data for metaproterenol not given.

Evidence Table 10. Metaproterenol vs terbutaline - RCTs: efficacy and safety

Chester, 1978 — Quality rating (Efficacy, Safety): Fair, NA

FEV1, maximum increase from baseline

Metaproterenol 1300ug		Terbutaline 500ug	
16	NR(NR)	16	NR(NR)
16	NR(NR)	16	NR(NR)
	NR(NR)		NR(NR)

Notes: Metaproterenol - maximum increase occurred at 15 min
Terbutaline - maximum increase occurred at 2 hrs. Also only intervention that had effect sustained at four hours, although only stated as >15%, value not given.

Other Efficacy/Effectiveness Outcomes and Comments:

Most data presented in graphical form only, making quantitative comparisons impossible.

Other Adverse Events and Comments:

NR

Evidence Table 11. Fenoterol vs metaproterenol - RCTs: efficacy and safety

Burgess, 1990 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Country: New Zealand

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 12	0	/ 0	/ 12

Inclusion criteria:
Stable asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** NR years
Gender: 58.33% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol	NR	12	NR	58.33% Female
Metaproterenol	NR	12	NR	58.33% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	0.65(NR)		0.72(NR)

Notes: Data not reported, estimated from graph.

FEV1

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	0.55(NR)		0.58(NR)

Notes: Data not reported, estimated from graph.

Evidence Table 11. Fenoterol vs metaproterenol - RCTs: efficacy and safety

Burgess, 1990 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	0.4(NR)		0.4(NR)

Notes: Data not reported, estimated from graph.

Other Efficacy/Effectiveness Outcomes and Comments:

FEV1: there is no significant difference between fenoterol and metaproterenol

Adverse Events:

DBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	-7.7(8.66)		-3.9(9.01)

SBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	7.8(6.93)		3.9(9.7)

DBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	-4.9(5.54)		-3.6(5.89)

SBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	3.3(10.39)		1.1(8.31)

Evidence Table 11. Fenoterol vs metaproterenol - RCTs: efficacy and safety

Burgess, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

DBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	-1.2(3.12)		-0.9(5.54)

SBP, mean change

Fenoterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	-1.2(8.66)		2.6(7.97)

Other Adverse Events and Comments:

Plasma K+: fenoterol significantly decreased plasma K+ at 65 & at 90min when compared w/ the other agents.

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Anderson, 1979 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: UK

Sample:

# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
NR	NR	17	NR	NR	17

Inclusion criteria:
Patients with bronchial asthmas were studied. All showed an improvement in peak expiratory flow rate (PEFR) exceeding 20% 5 min after inhaling 2 puffs (016mg) of isoprenaline. Informed consent.

Exclusion criteria:
NR

Comments:
3 day crossover - patients randomized to fenoterol, terbutaline or placebo on each of three days.

Population: **Mean age:** 52 years
Gender: 35.29% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 0.4mg	NR	17	52 years	35.29% Female
Terbutaline 0.5mg	NR	17	52 years	35.29% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Effectiveness Outcomes:

Breathing scores, very much better

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	2(12)	17	1(6)
	NR(NR)		NR(NR)

Breathing scores, much better

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	2(12)	17	2(12)
	NR(NR)		NR(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Anderson, 1979 — Quality rating (Efficacy, Safety): Fair, Fair

Breathing scores, a little better

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	5(29)	17	6(35)
	NR(NR)		NR(NR)

Breathing scores, no change

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	3(18)	17	7(41)
	NR(NR)		NR(NR)

Breathing scores, worse

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	0(0)	17	1(6)
	NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

PEFR - reported in graphical form only. Fenoterol curve reported as significantly higher than either terbutaline ($p<0.05$) or placebo ($p<0.01$) for all timepoints

Breathing scores subjectively reported by patients

Adverse Events:

Chest pain

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	1(6)	17	2(12)
	NR(NR)		NR(NR)

Fainting and diarrhea

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	0(0)	17	1(6)
	NR(NR)		NR(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Anderson, 1979 — Quality rating (Efficacy, Safety): Fair, Fair

Light-headedness

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	2(12)	17	2(12)
	NR(NR)		NR(NR)

Difficulty focusing

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	1(6)	17	0(0)
	NR(NR)		NR(NR)

Tremor, tinnitus

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	0(0)	17	1(6)
	NR(NR)		NR(NR)

Tremor

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	1(6)	17	0(0)
	NR(NR)		NR(NR)

Cough

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	1(6)	17	0(0)
	NR(NR)		NR(NR)

Husky voice

Fenoterol 0.4mg		Terbutaline 0.5mg	
17	NR(NR)	17	NR(NR)
17	1(6)	17	0(0)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Gray, 1982 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** 1 day days **Setting:** Community practice
Country: UK

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	12	0 /	0 /	12

Inclusion criteria:

Stable asthmatic pts attending the Asthma Clinic at King's College Hospital took part in the trial. All patients had previously shown at least 20% increase in FEV1 after inhaled beta-agonist, and all were taking inhaled beta-agonist regularly (salbutamol,

Exclusion criteria:

NR

Comments:

Study duration - 3 (nonconsecutive) days

Population: **Mean age:** 33 years
Gender: 58.33% Female

Intervention:

Duration: 3 day

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 100ug	NR	12	33 years	58.33% Female
Terbutaline 250ug	NR	12	33 years	58.33% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean increase following first dose

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	NR(NR)		NR(NR)

Notes: Baseline values not reported

FEV1, % of maximum response

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	NR(NR)		NR(NR)

Fenoterol 100ug vs Terbutaline 250ug, p value: <0.01

Notes: FEV1 values declined steadily for both drugs once maximum increase was reached. Measures of FEV1 every 30 minutes found no statistically significant difference between the two drugs until 4 hrs following maximum increase.

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Gray, 1982 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, % of maximum response

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	NR(NR)		NR(NR)

Fenoterol 100ug vs Terbutaline 250ug, p value: <0.005

FEV1, % of maximum response

NR	NR(NR)
NR	NR(NR)
	NR(NR)

Fenoterol 100ug vs Terbutaline 250ug, p value: <0.005

FEV1, mean maximum peak response

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	NR(NR)		NR(NR)

Notes: Values represent % increase from baseline (values not reported) following maximum dose 15 puffs of each drug p >0.5

Other Efficacy/Effectiveness Outcomes and Comments:

Fenoterol caused increase in heart rate significantly higher than terbutaline for all timepoints once dosage of 7 puffs reached (fig. 5 in text)

Adverse Events:

Heart rate, mean maximum increase

Fenoterol 100ug		Terbutaline 250ug	
12	85(NR)	12	84(NR)
12	NR(NR)	12	NR(NR)
	6.3(NR)		2.4(NR)

Heart rate, mean maximum increase

Fenoterol 100ug		Terbutaline 250ug	
12	85(NR)	12	84(NR)
12	NR(NR)	12	NR(NR)
	25(NR)		15(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Gray, 1982 — Quality rating (Efficacy, Safety): Fair, Fair

Palpitations

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	6(50)	12	1(8.3)
	NR(NR)		NR(NR)

Notes: Mean heart rate of all patients reporting palpitations (not divided by intervention): 118 bpm (SE 4.1 bpm)

Tremor

Fenoterol 100ug		Terbutaline 250ug	
12	NR(NR)	12	NR(NR)
12	3(25)	12	1(8.3)
	NR(NR)		NR(NR)

Notes: 2 of fenoterol patients reported tremor following cumulative dose of 8 puffs, all other tremors reported following maximum cumulative 15 puffs for both drugs.

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Lawford, 1987 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: RCT DB Crossover **Run-in :**

Setting: Community practice

Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 18	NR	/ NR	/ NR

Inclusion criteria:

Asthmatic patients regularly attending outpatient clinic

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 56 years

Gender: NR% Female

Intervention:

Duration: 2 days

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 200ug	400ug	18	56 years	NR
Terbutaline 250ug	500ug	18	56 years	NR

Outcomes:

Reporting of data is as follows:

Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Fenoterol 200ug		Terbutaline 250ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	0.39(NR)		0.24(NR)

FEV1, mean change

Fenoterol 200ug		Terbutaline 250ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	0.22(NR)		0.04(NR)

FEV1, mean change

Fenoterol 200ug		Terbutaline 250ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	0.22(NR)		0.04(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Lawford, 1987 — Quality rating (Efficacy, Safety): Fair, NA

FEV1, mean change

Fenoterol 200ug		Terbutaline 250ug	
NR	NR(NR)	NR	NR(NR)
NR	NR(NR)	NR	NR(NR)
	0.35(NR)		0.24(NR)

Notes: Baseline values not stratified by drug. Reported as 1.58 on day 1 and 1.60 on day 2.

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Lin, 2002 — Quality rating (Efficacy, Safety): NA, Fair

Design:

Study design: RCT NR NR **Run-in :** **Setting:** Emergency
Country: Taiwan

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	108	0 /	0 /	108

Inclusion criteria:

Patients who presented to the emergency department and pediatric allergy clinic of the Taipei Municipal Chung Hsias Hospital with a diagnosis of acute asthma, or of acute exacerbation of chronic asthma were enrolled in this study. The asthma diagnosis was

Exclusion criteria:

Patients with complications of pneumonia, congestive heart failure, foreign body aspiration, or bronchopulmonary dysplasia were excluded. Patients who had received any aerosolized beta-agonist within 12h before presentation were also excluded.

Comments:

Population: **Mean age:** 8.14 years
Gender: 44.44% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 1.25mg	NR	57	8.11 years	45.61% Female
Terbutaline 5.0mg	NR	51	8.18 years	43.14% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Heart rate

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	108.68(17.5)	51	113.18(18.20)
57	113.09(14.9)	51	102.51(18.20)
	4.41(NR)		7.33(NR)

Palpitations

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	NR(NR)	51	NR(NR)
57	4(7.0)	51	3(5.9)
	NR(NR)		NR(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Lin, 2002 **Quality rating (Efficacy, Safety): NA, Fair**

Headache

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	NR(NR)	51	NR(NR)
57	1(1.8)	51	2(3.9)
	NR(NR)		NR(NR)

Dizziness

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	NR(NR)	51	NR(NR)
57	6(10.5)	51	6(11.8)
	NR(NR)		NR(NR)

Weakness of extremities

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	NR(NR)	51	NR(NR)
57	1(1.8)	51	1(2.0)
	NR(NR)		NR(NR)

Tremor

Fenoterol 1.25mg		Terbutaline 5.0mg	
57	NR(NR)	51	NR(NR)
57	3(5.3)	51	3(5.9)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Country: Romania

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	63	0 /	0 /	63

Inclusion criteria:
Chronic bronchitis (CIBA Guest Symposium and American Thoriacic Society criteria); a response of the FEV1 of at least 10% of baseline values 30 minutes after inhalation of 1500 ug orciprenaline aerosol

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 56.5 years
Gender: 25.4% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 400ug	NR	63	56.5 years	25.4% Female
Terbutaline 500ug	NR	63	56.5 years	25.4% Female
Fenoterol 400ug	NR	63	56.5 years	25.4% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	0.325(NR)		0.305(NR)		0.285(NR)

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Manicatide, 1978 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1

Albuterol 400ug		Fenoterol 400ug		Terbutaline 500ug	
63	NR(NR)	63	NR(NR)	63	NR(NR)
63	NR(NR)	63	NR(NR)	63	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Effectiveness Outcomes:

Preference

Albuterol 400ug		Terbutaline 500ug		Fenoterol 400ug		No preference	
63	NR(NR)	63	NR(NR)	63	NR(NR)	63	NR(NR)
63	19(30.2)	63	16(25.4)	63	21(33.3)	63	7(11.1)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

VC

NR

Other Adverse Events and Comments:

No significant changes in HR.
No significant changes in BP.

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Ribeiro, 1990 **Quality rating (Efficacy, Safety): Fair, Fair**

Design:

Study design: RCT Open Crossover **Run-in :**

Setting: NR

Country: Sweden

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	40	4 /	0 /	36

Inclusion criteria:

Patients fulfilled all the following inclusion criteria: chronic stable asthma, reversibility > 15% after inhalation of 0.5mg terbutaline or equivalent from an MDI.

Exclusion criteria:

None of the children had pulmonary disease other than asthma, significant cardiac disease, hyperthyroidism, insulin-dependent diabetes or any ongoign infection. None of the children had any previous experience of either of the two study inhalers.

Comments:

Population: **Mean age:** 9 years

Gender: 30.56% Female

Intervention:

Duration: Single dose, 2 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 0.2mg TID	0.6mg	NR	NR	NR
Terbutaline 0.5mg TID	1.5mg	NR	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC, 30 min after inhalation

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.76(0.39)	36 1.83(0.40)
36 1.97(0.39)	36 2.04(0.39)
NR(NR)	NR(NR)

FVC, 15 min after inhalation

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.76(0.39)	36 1.83(0.40)
36 1.93(0.40)	36 1.99(0.39)
NR(NR)	NR(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Ribeiro, 1990 — Quality rating (Efficacy, Safety): Fair, Fair

FEV1, 30 min after inhalation

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.34(0.33)	36 1.38(0.36)
36 1.64(0.32)	36 1.71(0.33)
NR(NR)	NR(NR)

FEV1, 15 min after inhalation

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.34(0.33)	36 1.38(0.36)
36 1.59(0.32)	36 1.63(0.32)
NR(NR)	NR(NR)

PEF, mean increase

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 NR(NR)	36 NR(NR)
36 NR(NR)	36 NR(NR)
44(25)	41(20)

PEF, mean increase

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 NR(NR)	36 NR(NR)
36 NR(NR)	36 NR(NR)
50(28)	46(25)

FVC, baseline

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.61(0.39)	36 1.61(0.39)
36 NR(NR)	36 NR(NR)
NR(NR)	NR(NR)

FEV1, baseline

Fenoterol 0.2mg TID	Terbutaline 0.5mg TID
36 1.25(.035)	36 1.25(0.35)
36 NR(NR)	36 NR(NR)
NR(NR)	NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Mean asthma symptom scores:
fenoterol - 0.23 (am) and 0.22 (pm)
terbutaline - 0.17 (am) and 0.13 (pm)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Ribeiro, 1990 — Quality rating (Efficacy, Safety): Fair, Fair

Explanation of FEV1 (baseline) and FVC (baseline)-
0.5 mg terbutaline inhaled prior to baseline measure at start of study.

Adverse Events:

Tremor

Fenoterol 0.2mg TID		Terbutaline 0.5mg TID	
36	NR(NR)	36	NR(NR)
36	2(5.6)	36	0(0)
	NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 — Quality rating (Efficacy, Safety): Fair, Fair

Design:

Study design: RCT SB Parallel **Run-in :** **Setting:** NR
Country: Brazil

Sample:	# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
	NR	NR	21	NR	NR	21

Inclusion criteria:
Children presenting with acute bronchial asthma and demonstrated an FEV1 lower than 80% of nromal predicted value.

Exclusion criteria:
Children should not have taken long-acting theophylline, antihistamines, or corticosteroids for 24 hr and beta-adrenergic agents or other bronchodilator medication for 12 hr before the study.

Comments:

Population: **Mean age:** 10.41 years
Gender: 42.86% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 5mg	NR	11	NR	NR
Fenoterol 0.083mg/kg	NR	14	NR	NR
Terbutaline 0.1mg/kg	NR	12	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

FEV1, mean % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 1.04(0.53)	21 1.18(0.50)	21 0.94(0.44)
21 NR(NR)	21 NR(NR)	21 NR(NR)
NR(NR)	NR(NR)	NR(NR)

Notes: Figures interpolated from graph in text.

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 **Quality rating (Efficacy, Safety): Fair, Fair**

FEV1, mean % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Bronchodilator effect, mean duration

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg			
21	NR(NR)	21	NR(NR)	21	NR(NR)	21	NR(NR)
21	365(NR)	21	287(NR)	21	NR(NR)	21	285(NR)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

<u>Other Efficacy/Effectiveness Outcomes and Comments:</u>

Figures interpolated from graph in text.

<u>Adverse Events:</u>

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.

Heart rate, % change from baseline

Albuterol 5mg		Fenoterol 0.083mg/kg		Terbutaline 0.1mg/kg	
21	NR(NR)	21	NR(NR)	21	NR(NR)
21	NR(NR)	21	NR(NR)	21	NR(NR)
	NR(NR)		NR(NR)		NR(NR)

Notes: Figures interpolated from graph in text.
3/11 (27%) of albuterol patients had larger HR increases (36, 60 and 70 bpm respectively); 2/14 (14%) of fenoterol patients had larger heart r increases (38 & 60 bpm)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Scalabrin, 1996 — Quality rating (Efficacy, Safety): Fair, Fair

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
93(NR)	86(NR)	104(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
106(NR)	34(NR)	90(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
151(NR)	93(NR)	62(NR)

Notes: Figures interpolated from graph in text.

Tremor, % change from baseline

Albuterol 5mg	Fenoterol 0.083mg/kg	Terbutaline 0.1mg/kg
21 NR(NR)	21 NR(NR)	21 NR(NR)
21 NR(NR)	21 NR(NR)	21 NR(NR)
175(NR)	167(NR)	119(NR)

Notes: Figures interpolated from graph in text.

Other Adverse Events and Comments:

NR

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Tammivaara, 1979 **Quality rating (Efficacy, Safety): NA, Poor**

Design:

Study design: RCT NR NR **Run-in :** NR **Setting:** NR

Country: Finland

Sample:

# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
NR	/ NR	/ 11	NR	/ NR	/ 11

Inclusion criteria:

NR

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 35.5 years

Gender: NR% Female

Intervention:

Duration: NR NR

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol	NR	NR	NR	NR
Terbutaline	NR	NR	NR	NR

Outcomes:

Reporting of data is as follows:

Drug Name

n Baseline

n Follow-up

Mean Difference

Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

During exercise with placebo PEF increased from 439 +- 42 (M +- SD) with 15%, during terbutaline from 420+-45 with 11%, and during fenoterol from 419+-50 with 18%. The mean of the lowest PEF without medication wass -34% 14 min and during placebo correspondingly -39% 10 min after exercise. During terbutaline the mean of the lowest PEF seen 14 min after exercise only returned back to the initial level and during fenoterol it was never less than 6% higher as late as 18 min after exercise.

Other Adverse Events and Comments:

No side effects were reported. There were NSDs in maximal HR, BP or breathing frequency during placebo or drugs used.

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Trembath, 1979 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: RCT DB Crossover **Run-in :** 2 wk days **Setting:** Community practice
Country: UK

Sample: # Screened / Eligible / Enrolled # Withdrawn / Lost to follow-up / Analyzed
NR / NR / 23 7 / 1 / unclear

Inclusion criteria:
FEV1 <80% of predicted value and minimum of 15% improvement in FEV1 following isoproterenol inhalation.

Exclusion criteria:
NR

Comments:
Unclear if analysis includes 7 withdrawals.

Population: **Mean age:** 44.7 years
Gender: 56.52% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol	5.36 puffs/day	23	44.7 years	56.52% Female
Terbutaline	5.34 puffs/day	23	44.7 years	56.52% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FVC

Fenoterol		Terbutaline	
23	3.40(1.27)	23	3.40(1.27)
23	3.66(NR)	23	3.85(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: NS

PEFR

Fenoterol		Terbutaline	
23	328.0(89.4)	23	328.0(89.4)
23	359.1(NR)	23	351.7(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: NS

FEV1

Fenoterol		Terbutaline	
23	2.25(0.69)	23	2.25(0.69)
23	2.56(NR)	23	2.61(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: NS

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Trembath, 1979 — Quality rating (Efficacy, Safety): Fair, Poor

FVC

Fenoterol		Terbutaline	
23	3.40(1.27)	23	3.40(1.27)
23	3.73(NR)	23	3.88(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: NS

PEFR

Fenoterol		Terbutaline	
23	328.0(89.4)	23	328.0(89.4)
23	315.7(NR)	23	385.0(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: <0.001

FEV1

Fenoterol		Terbutaline	
23	2.25(0.69)	23	2.25(0.69)
23	2.43(NR)	23	2.80(NR)
	NR(NR)		NR(NR)

Fenoterol vs Terbutaline, p value: <0.06

Effectiveness Outcomes:

Preference

Fenoterol		Terbutaline		No preference	
23	NR(NR)	23	NR(NR)	23	NR(NR)
15	6(40)	15	7(46.7)	15	2(13.3)
	NR(NR)		NR(NR)		NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

No serious AEs reported. Tremor reported in one fenoterol & one terbutaline patient.
Seven withdrawals (n=5 fenoterol, n=2 terbutaline) due to lack of efficacy

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 — Quality rating (Efficacy, Safety): Fair, Good

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** Research Center
Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 10	NR	/ NR	/ 10

Inclusion criteria:
Asthma

Exclusion criteria:
NR

Comments:

Population: **Mean age:** NR years
Gender: 20% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 100ug	2,600 ug	10	NR	20% Female
Fenoterol 200ug	5,200 ug	10	NR	20% Female
Terbutaline 250ug	6,500 ug	10	NR	20% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.63(NR)		0.76(NR)		0.63(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.98(NR)		1.05(NR)		1.10(NR)

FEV1, mean change

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.87(NR)		1.10(NR)		0.92(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 — Quality rating (Efficacy, Safety): Fair, Good

Other Efficacy/Effectiveness Outcomes and Comments:

Mean area under the curve - within subject differences for fenoterol vs albuterol(SE) and terbutaline(SE):
FEV1 - fenoterol 1.77; albuterol -0.16 (0.15); terbutaline -0.08 (0.15)
Potassium concentration - fenoterol -0.82; albuterol 0.54 (0.17); terbutaline 0.33(0.18)

All values interpolated from graphs in text

Adverse Events:

Heart rate, mean maximum change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	8(9)		29(24)		8(14)

Palpitations

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	1(10)	10	3(30)	10	3(30)
	NR(NR)		NR(NR)		NR(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	0.10(NR)		0.06(NR)		0.03(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.42(NR)		-0.73(NR)		-0.45(NR)

K+, concentration change from baseline

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	NR(NR)	10	NR(NR)	10	NR(NR)
	-0.01(NR)		-0.42(NR)		-0.20(NR)

Evidence Table 12. Fenoterol vs terbutaline - RCTs: efficacy and safety

Wong, 1990 — Quality rating (Efficacy, Safety): Fair, Good

Headache

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	3(30)	10	5(50)	0	2(20)
	NR(NR)		NR(NR)		NR(NR)

Tremor

Albuterol 100ug		Fenoterol 200ug		Terbutaline 250ug	
10	NR(NR)	10	NR(NR)	10	NR(NR)
10	4(40)	10	6(60)	10	4(40)
	NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 13. Albuterol vs levalbuterol - Non-RCTs: safety only

Nowak, 2004 — Quality rating (Efficacy, Safety): Fair, for cohort, Fair

Design:

Study design: CT Open Parallel **Run-in :** NR **Setting:** Emergency
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	91	0 /	0 /	91

Inclusion criteria:

Asthmatic adults presenting to the ED (Henry Ford Hospital, Detroit, MI; MetroHealth Center, Cleveland OH) with a FEV1 of 20% to 55% predicted (decreased from 30-20% during enrollment)
Of the 0.63-mg levalbuterol group), O2 saturation >=90%, <10 pack-yea

Exclusion criteria:

Pregnant, hospitalized for asthma within 2 months, had fixed airway disease, or received racemic albuterol in the ED before enrollment

Comments:

Population: **Mean age:** 33 years
Gender: 54% Female

Intervention:

Duration: 3 doses in ER NR

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 2.5mg	three doses	14	32 years	64% Female
Albuterol 5.0mg	three doses	13	40 years	46% Female
Levalbuterol 0.63mg	three doses	12	31 years	58% Female
Levalbuterol 1.25mg	three doses	14	25 years	50% Female
Levalbuterol 2.5mg	three doses	12	33 years	58% Female
Levalbuterol 3.75mg	three doses	14	35 years	57% Female
Levalbuterol 5.0mg	three doses	12	32 years	42% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Effectiveness Outcomes:

Patients hospitalized

Albuterol 2.5mg		Albuterol 5.0mg		Levalbuterol 0.63mg		Levalbuterol 1.25mg		Levalbuterol 2.5mg		Levalbuterol 3.7	
14	NR(NR)	13	NR(NR)	12	NR(NR)	14	NR(NR)	12	NR(NR)	14	NR(NR)
14	1(7)	13	0(0)	12	0(0)	14	1(7)	12	1(8)	14	4(29)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)		NR(NR)

Levalbuterol 5.0mg

12 NR(NR)
12 1(8)
NR(NR)

Evidence Table 13. Albuterol vs levalbuterol - Non-RCTs: safety only

Nowak, 2004 — Quality rating (Efficacy, Safety): Fair, for cohort, Fair

Patients requiring additional therapy poststudy

Albuterol 2.5mg	Albuterol 5.0mg	Levalbuterol 0.63mg	Levalbuterol 1.25mg	Levalbuterol 2.5mg	Levalbuterol 3.7
14 NR(NR)	13 NR(NR)	12 NR(NR)	14 NR(NR)	12 NR(NR)	14 NR(NR)
14 6(43)	13 4(31)	12 1(8)	14 1(7)	12 3(25)	14 5(36)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

Levalbuterol 5.0mg
12 NR(NR)
12 1(8)
NR(NR)

Patients discharged after three doses

Albuterol 2.5mg	Albuterol 5.0mg	Levalbuterol 0.63mg	Levalbuterol 1.25mg	Levalbuterol 2.5mg	Levalbuterol 3.7
14 NR(NR)	13 NR(NR)	12 NR(NR)	14 NR(NR)	12 NR(NR)	14 NR(NR)
14 7(50)	13 8(62)	12 11(92)	14 12(86)	12 8(67)	14 5(36)
NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)

Levalbuterol 5.0mg
12 NR(NR)
12 10(83)
NR(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Plasma levels; FEV1

Not a RCT; efficacy outcomes excluded.

Adverse Events:

Heart rate, maximum change

Albuterol 2.5mg	Levalbuterol 1.25mg	Levalbuterol 5.0mg
14 NR(NR)	14 NR(NR)	12 NR(NR)
14 NR(NR)	14 NR(NR)	12 NR(NR)
15(NR)	17(NR)	35(NR)

Notes: Other heart rates: NR; 'changes in glucose, potassium, and HR were proportional to the dose.. And chagnes were similar after match doses of levalbuterol and racemic albuterol

Glucose, maximum change

Albuterol	Levalbuterol
16 NR(NR)	18 NR(NR)
16 NR(NR)	18 NR(NR)
15.9-62.4(NR)	46.4-57.1(NR)

Evidence Table 13. Albuterol vs levalbuterol - Non-RCTs: safety only

Nowak, 2004 **Quality rating (Efficacy, Safety): Fair, for cohort, Fair**

K+, maximum change

Albuterol		Levalbuterol	
27	NR(NR)	22	NR(NR)
27	NR(NR)	22	NR(NR)
	-0.52 to -		-0.29 to -

Other Adverse Events and Comments:

NR

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Choo-Kang, 1969 — Quality rating (Efficacy, Safety): Fair, Poor

Design:

Study design: CT DB Crossover **Run-in :** NR **Setting:** NR
Country: UK

Sample:

# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
NR	NR	24	NR	NR	NR

Inclusion criteria:
Stabilized for at least 6 mos w/corticosteroid use (generally prednisolone)

Exclusion criteria:
NR

Comments:

Population: **Mean age:** 56.3 years
Gender: 70.83% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 200ug	200ug	24	56.3 years	70.83% Female
Metaproterenol 1500ug	1500ug	24	56.3 years	70.83% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1, % above control value

Albuterol 200ug	Metaproterenol 1500ug
24 NR(NR)	24 NR(NR)
24 NR(NR)	24 NR(NR)
26(NR)	19(NR)

FEV1, maximum mean increase

Albuterol 200ug	Metaproterenol 1500ug
24 NR(NR)	24 NR(NR)
24 NR(NR)	24 NR(NR)
47.7(NR)	38.7(NR)

Other Efficacy/Effectiveness Outcomes and Comments:

Area under the curve - integrated FEV1 change:
albuterol - 110,800
metaproterenol - 93,900
(authors indicate that a difference of 24,000 or more is significant at 5%level)

Area under the curve - integrated FVC change:
albuterol - 160,000
metaproterenol - 126,200
(authors indicate that a difference of 40,500 or more is significant at the 5% level)

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Choo-Kang, 1969 — Quality rating (Efficacy, Safety): Fair, Poor

NR

Adverse Events:

Heart rate, mean % change

Albuterol 200ug		Metaproterenol 1500ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	3.5(NR)		1.6(NR)

Heart rate, mean % change

Albuterol 200ug		Metaproterenol 1500ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	0.5(NR)		1.1(NR)

Heart rate, mean % change

Albuterol 200ug		Metaproterenol 1500ug	
24	NR(NR)	24	NR(NR)
24	NR(NR)	24	NR(NR)
	4.1(NR)		-0.6(NR)

Other Adverse Events and Comments:

NR

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Freisleben, 1971 — Quality rating (Efficacy, Safety): NA, Poor

Design:

Study design: CT NR NR **Run-in :** NR **Setting:** NR
Country: Austria

Sample:

# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
NR	NR	25	NR	NR	25

Inclusion criteria:
Patients (aged 10 - 70) who experienced moderate to severe chronic airways disease with some degree of reversibility

Exclusion criteria:
NR

Comments:

Population: **Mean age:** NR years
Gender: NR% Female

Intervention:

Duration: NR NR

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	NR	NR	NR	NR
Metaproterenol	NR	NR	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

Not included for efficacy

Other Adverse Events and Comments:

Only AE reporting : "In all these 25 cases we had not one undesirable side-effect & none noted tachycardia or other symptoms."

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Milner, 1971 **Quality rating (Efficacy, Safety): Fair, Poor**

Design:

Study design: CT DB Crossover **Run-in :** NR **Setting:** Community practice

Country: UK

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 12	NR	/ NR	/ 12

Inclusion criteria:

All attended the asthma clinic of The Hospital for Sick Children. All the children had had symptoms of asthma for over seven years.

Exclusion criteria:

NR

Comments:

Assume no withdrawals

Population: **Mean age:** 11.8 years

Gender: 50% Female

Intervention:

Duration: Single dose NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	1.5 ml/.5%	12	11.8 years	50% Female
Metaproterenol	1.5 ml/2.5%	12	11.8 years	50% Female

Outcomes:

Reporting of data is as follows:

Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV0-75, mean change at peak

Albuterol		Metaproterenol	
12	0.968(NR)	12	0.822(NR)
12	0.446(NR)	12	0.536(NR)
	0.446(NR)		0.536(NR)

Notes: Difference required for significance: 186 (p=0.05)

FVC, duration

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	73(NR)	12	85(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 30 min

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Milner, 1971 **Quality rating (Efficacy, Safety): Fair, Poor**

FVC, time to peak

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	57(NR)	12	54(NR)
	NR(NR)		NR(NR)

Notes: DIfference required for significance: 38 min

FEV0-7, duration

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	84(NR)	12	96(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 25 min (p=0.05)

FEV0-75, AUC

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	48(NR)		53(NR)

Notes: Differnce required for significance: 22 l/min (p=0.05)

FEV0-75, time of peak

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	68(NR)	12	63(NR)
	68(NR)		63(NR)

Notes: Difference required for significance: 36 min (p=0.05)

FVC, AUC

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	50(NR)	12	45(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 22 l/min

FVC, mean change at peak

Albuterol		Metaproterenol	
12	1.837(NR)	12	1.771(NR)
12	2.301(NR)	12	2.224(NR)
	0.464(NR)		0.453(NR)

Notes: Difference required for significance: 149 ml (p=0.05)

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Milner, 1971 — Quality rating (Efficacy, Safety): Fair, Poor

Other Efficacy/Effectiveness Outcomes and Comments:

FEV0-75

NR

Adverse Events:

DBP, duration

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	28(NR)	12	22(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 19 min (p=0.05)

DBP, AUC

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	214(NR)	12	94(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 157 mm/min (p=0.05)

DBP, time to peak

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	10(NR)	12	26(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 24 min (p=0.05)

SBP, AUC

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	409(NR)	12	555(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 327 mm/min (p=0.05)

SBP, time to peak

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	29(NR)	12	10(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 30 min (p=0.05)

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Milner, 1971 **Quality rating (Efficacy, Safety): Fair, Poor**

DBP, increase from baseline

Albuterol		Metaproterenol	
12	60(NR)	12	63(NR)
12	63(NR)	12	66(NR)
	3(NR)		3(NR)

Notes: Difference required for significance: 3 mmHg (p=0.05)

SBP, increase from baseline

Albuterol		Metaproterenol	
12	97(NR)	12	98(NR)
12	106(NR)	12	111(NR)
	9(NR)		13(NR)

Notes: Difference required for significance : 6 mmHg (p=0.05)

Pulse rate, mean duration of increase

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	45(NR)	12	42(NR)
	NR(NR)		NR(NR)

Notes: DIfference required for significance: 19 min (p=0.05)

Pulse rate, AUC

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	908(NR)	12	1427(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 784 bpm (p=0.05)

Pulse rate, time to peak

Albuterol		Metaproterenol	
12	NR(NR)	12	NR(NR)
12	20(NR)	12	20(NR)
	NR(NR)		NR(NR)

Notes: Difference required for significance: 27 min (p=0.05)

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Milner, 1971 — Quality rating (Efficacy, Safety): Fair, Poor

Pulse rate, increase from baseline

Albuterol		Metaproterenol	
12	101(NR)	12	107(NR)
12	118(NR)	12	135(NR)
	17(NR)		28(NR)

Notes: Difference required for significance: 11 bpm (p=0.05)

Dizziness

Metaproterenol	
12	NR(NR)
12	1(8.3)
	NR(NR)

Notes: no further data given

Other Adverse Events and Comments:

NR

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Peacock, 1992 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 22	4	/ 0	/ 22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 14. Albuterol vs metaproterenol - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Other Adverse Events and Comments:

NR

Evidence Table 15. Albuterol vs pirbuterol - Non-RCTs: safety only

Peacock, 1992 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
	NR	/ NR	/ 22	4	/ 0	/ 22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 15. Albuterol vs pirbuterol - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Other Adverse Events and Comments:

NR

Evidence Table 16. Metaproterenol vs pirbuterol - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	4 /	0 /	22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 16. Metaproterenol vs pirbuterol - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Other Adverse Events and Comments:

NR

Evidence Table 17. Albuterol vs fenoterol - Non-RCTs: safety only

Garrett, 1996 — Quality rating (Efficacy, Safety): NA, Fair

Design:

Study design: Cohort NR NR **Run-in :** NA **Setting:** Emergency
Country: New Zealand

Sample: # Screened / Eligible / Enrolled # Withdrawn / Lost to follow-up / Analyzed
NA / 725 / NA NA / NA / 655

Inclusion criteria:
Asthma aged 15-55 years who attended a single Auckland, New Zealand hospital for acute asthma between Jan 1 1986 and Dec 21 1987.

Exclusion criteria:
Persons using salbutamol and fenoterol concomitantly, users of other B agonists, and non-users of B agonists

Comments:
Retrospective cohort study; Followed up until death or May 31 1989 for the occurrence of severe life-threatening event (ICU admission) or death due to asthma.

Population: **Mean age:** NR years
Gender: 64% Female

Intervention:

Duration: Cohort (3.5y) NA

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	NR	455	NR	NR
Fenoterol	NR	176	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Other Adverse Events and Comments:

There were 105 severe life threatening attacks among 6 patinets comprising 90 admissions to ICU & 15 asthma deaths.
- RR for severe life threatening attacks & death comparing inhaled fenoterol w/ inhaled albuterol:
  - none: 2.1 (1.37 to 3.13)
  - admission in the past yr & any oral steroid use at previous hospital attendance: 1.5 (0.99 to 2.26)
  - number of prior admissions during study period & continuous oral steroid use at previous hospital attendance: 1.3 (0.82 to 1.91)
  - number of prior admissions during study period, race, & continuous oral steroid use at previous hospital attendance: 1.0 (0.63 to 1.73)
- Unadjusted RR for severe life threatening asthma & death: comparison w/ inhaled albuterol
  - None: 1.3 (0.3 to 3.7)
  - Albuterol: 1.0
  - Fenoterol: 2.1 (1.4 to 3.1)
  - Fenoterol 200 ug: 1.9 (1.2 to 3.0)
  - Fenoterol 100 ug + itratoprium: 2.8 (1.4 to 5.1)

Evidence Table 17. Albuterol vs fenoterol - Non-RCTs: safety only

Spitzer, 1992 — Quality rating (Efficacy, Safety): NA, Good

Design:

Study design: Cohort NA NR **Run-in :** NA **Setting:** NA
Country: Canada

Sample:

# Screened	Eligible	Enrolled	# Withdrawn	Lost to follow-up	Analyzed
NA	NA	NA	NA	NA	12,301

Inclusion criteria:

Date range: 1978-1987
Entrance into study based on: date of 10th dispensed prescription OR patient's 5th birthday OR January 1, 1980 (whichever date was the latest was used)

Exclusion criteria:

Exit from study based on: date of 55th birthday OR date of outcome event (fatal or near-fatal asthma) OR exit from province OR April 30, 1987 (whichever date was earliest)

Comments:

Computer files of Saskatchewan Prescription Drug Plan searched for asthma prescriptions. Each event (fatal or near-fatal asthma based on hypercarbia, nonelective intubation or both) compared with up to 8 matched controls,.

Population: **Mean age:** NR years
Gender: NR% Female

Intervention:

Duration: Case control NR

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol	NR	NR	NR	NR
Fenoterol	NR	NR	NR	NR

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

Death, odds ratio, high usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	29.4(NR)	NR	90.0(NR)
	NR(NR)		NR(NR)

Notes: High usage (n of canisters dispensed/12 mos)
albuterol: >/= 25
fenoterol: >/= 13 (adjusted for dose equivalence)

Evidence Table 17. Albuterol vs fenoterol - Non-RCTs: safety only

Spitzer, 1992 — Quality rating (Efficacy, Safety): NA, Good

Death, odds ratio, medium usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	10.0(NR)	NR	9.0(NR)
	NR(NR)		NR(NR)

Notes: Medium usage (n of canisters dispensed/12 mos)
albuterol: 13-24
fenoterol: 7-12 (adjusted for dose equivalence)

Death, odds ratio, low usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	3.4(NR)	NR	3.1(NR)
	NR(NR)		NR(NR)

Notes: Low usage (n of dispensed canisters/12 mos)
albuterol 1-12
fenoterol 1-6 (adjusted for dose equivalence)

Near-fatal event/death, odds ratio, high usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	24.0(NR)	NR	22.7(NR)
	NR(NR)		NR(NR)

Notes: High usage (n of canisters dispensed over 12 mos):
albuterol >/= 25
fenoterol >/= 13 (adjusted for dose equvalence)

Near-fatal event/death, odds ratio, medium usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	8.0(NR)	NR	7.8(NR)
	NR(NR)		NR(NR)

Notes: Medium usage (n of canisters dispensed over 12 mos):
albuterol 13 - 24
fenoterol 7 - 12 (adjusted for dose equivalence)

Near-fatal event/death, odds ratio, low usage*

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	4.4(NR)	NR	3.2(NR)
	NR(NR)		NR(NR)

Notes: Low usage (n of canisters dispensed over 12 mos):
1-12 canisters albuterol
1-6 canisters fenoterol (adjusted for dose equivalence)

Evidence Table 17. Albuterol vs fenoterol - Non-RCTs: safety only

Spitzer, 1992 — Quality rating (Efficacy, Safety): NA, Good

Near-fatal event/death, crude odds ratio

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	1.5(NR)	NR	3.7(NR)
	NR(NR)		NR(NR)

Death only, crude odds ratio

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
NR	0.9(NR)	NR	5.3(NR)
	NR(NR)		NR(NR)

Near-fatal event/ death, adjusted odds ratio

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
129	1.5(NR)	129	3.7(NR)
	NR(NR)		NR(NR)

Notes: CI (95%)
albuterol: 2.1 - 8.0
fenoterol: 3.1 - 12.2

Death only, adjusted odds ratio

Albuterol		Fenoterol	
NR	NR(NR)	NR	NR(NR)
44	0.9(NR)	44	5.3(NR)
	NR(NR)		NR(NR)

Notes: CI (95%)
albuterol: 1.0 - 7.6
fenoterol: 3.0 - 28.1

Other Adverse Events and Comments:

Combined baseline characteristics for both interventions: Death &/or near-fatal event: 129 cases (54% M), 655 controls (56% M), Death only: 44 cases (64% M), 233 controls (56% M).

Evidence Table 18. Albuterol vs terbutaline - Non-RCTs: safety only

Peacock, 1992 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	4 /	0 /	22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 18. Albuterol vs terbutaline - Non-RCTs: safety only

Peacock, 1992	Quality rating (Efficacy, Safety): Fair, NA

Other Adverse Events and Comments:

NR

Evidence Table 19. Metaproterenol vs terbutaline - Non-RCTs: safety only

Peacock, 1992 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	4 /	0 /	22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 19. Metaproterenol vs terbutaline - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Other Adverse Events and Comments:

NR

Evidence Table 19. Metaproterenol vs terbutaline - Non-RCTs: safety only

Roth, 1977 — Quality rating (Efficacy, Safety): NA, Poor

Design:

Study design: CT DB Crossover **Run-in :** NR **Setting:** Community practice
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	21	0 /	0 /	21

Inclusion criteria:

Ambulatory patients suffering from chronic moderate to severe asthmas who were either enrolled in the Allergy Clinic of the University of California, Irvine, Medical Center or a private practice in the area volunteered for the study. Forced expiratory vol

Exclusion criteria:

Subjects with either presence of or a history of cardiac arrhythmia, myocardial, thyroid, liber, kidney or other serious disease or a history of untoward reaction to sympathomimetic amines were eliminated from the study.

Comments:

Population: **Mean age:** 45 years
Gender: 61.9% Female

Intervention:

Duration: 3 puffs, 3 hrs

Drug name	Total daily dosage	N	Mean age	Gender
Metaproterenol 650ug	2040ug	21	45 years	61.9% Female
Terbutaline 125ug	375ug	21	45 years	61.9% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

NR

Adverse Events:

DBP

Metaproterenol 650ug		Terbutaline 125ug
21	NR(NR)	21 NR(NR)
21	NR(NR)	21 NR(NR)
	NR(NR)	NR(NR)

Notes: Both drugs reported to "slightly lower" diastolic blood pressure; no values were provided by the authors although they state difference not statistically significant.

Heart rate

Metaproterenol 650ug		Terbutaline 125ug
21	NR(NR)	21 NR(NR)
21	NR(NR)	21 NR(NR)
	NR(NR)	NR(NR)

Notes: Terbutaline produced a HR lower than baseline and both drugs slightly lowered DBP (over 6 hours; exact time NR)

Evidence Table 19. Metaproterenol vs terbutaline - Non-RCTs: safety only

Roth, 1977	Quality rating (Efficacy, Safety): NA, Poor

Other Adverse Events and Comments:

NR

Evidence Table 20. Fenoterol vs terbutaline - Non-RCTs: safety only

Carmichael, 1980 — Quality rating (Efficacy, Safety): NA, Fair/poor

Design:

Study design: CT DB NR **Run-in :** NR **Setting:** NR
Country: UK

Sample:

# Screened	/ Eligible	/ Enrolled	# Withdrawn	/ Lost to follow-up	/ Analyzed
NR	/ NR	/ 12	NR	/ NR	/ 12

Inclusion criteria:

Patients with stable chronic asthma in whom a greater than 25% increase in FEV1 was demostrated following the administration of salbutamol by IPPB were chosen for the study. All had base-line FEV1 values of less than 70% of the predicted normal. All regul

Exclusion criteria:

NR

Comments:

Population: **Mean age:** 51.8 years
Gender: 33.33% Female

Intervention:

Duration: NR NR

Drug name	Total daily dosage	N	Mean age	Gender
Fenoterol 0.5mg	NR	12	51.8 years	33.33% Female
Fenoterol 1mg	NR	12	51.8 years	33.33% Female
Fenoterol 2mg	NR	12	51.8 years	33.33% Female
Terbutaline 2.5mg	NR	12	51.8 years	33.33% Female
Terbutaline 5mg	NR	12	51.8 years	33.33% Female
Terbutaline 10mg	NR	12	51.8 years	33.33% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Other Efficacy/Effectiveness Outcomes and Comments:

Not assessed for efficacy

Adverse Events:

Heart rate, mean increase following max dose

Fenoterol 2mg		Terbutaline 10mg	
12	NR(NR)	12	NR(NR)
12	NR(NR)	12	NR(NR)
	4 bpm(NR)		9 bpm(NR)

Notes: Increase not statistically significant from each other or from baseline

Evidence Table 20. Fenoterol vs terbutaline - Non-RCTs: safety only

Carmichael, 1980 — Quality rating (Efficacy, Safety): NA, Fair/poor

Light-headedness

Terbutaline 5mg		Terbutaline 10mg	
12	NR(NR)	12	NR(NR)
12	1(8.3)	12	1(8.3)
	NR(NR)		NR(NR)

Tremor

Fenoterol 1mg		Fenoterol 2mg		Terbutaline 5mg		Terbutaline 10mg	
12	NR(NR)	12	NR(NR)	12	NR(NR)	12	NR(NR)
12	1(8.3)	12	5(41.7)	12	1(8.3)	12	3(25)
	NR(NR)		NR(NR)		NR(NR)		NR(NR)

Other Adverse Events and Comments:

NR

Evidence Table 21. Pirbuterol vs terbutaline - Non-RCTs: safety only

Peacock, 1992 — Quality rating (Efficacy, Safety): Fair, NA

Design:

Study design: CT Open Crossover **Run-in :** NR **Setting:** Research Center
Country: US

Sample:	# Screened /	Eligible /	Enrolled	# Withdrawn /	Lost to follow-up /	Analyzed
	NR /	NR /	22	4 /	0 /	22

Inclusion criteria:

Diagnosis of COPD;
Baseline FEV/FVC ratio <70%

Exclusion criteria:

Diagnosis of asthma or pulmonary disease other than COPD;
Oral steroid use within 1 mo. of enrollment;
Acute exacerbation of pulmonary symptoms within 2 mos. of enrollment;
Use of supplemental oxygen;
Routine use of nebulized bronchodilator therapy;

Comments:

Withdrawals due to: acute exacerbations of pulmonary symptoms that required steroid therapy (n=2), family issues (n=1), diagnosis of a metastatic malignancy (n=1)

Population: **Mean age:** 69 years
Gender: 31.82% Female

Intervention:

Duration: 4 weeks

Drug name	Total daily dosage	N	Mean age	Gender
Albuterol 0.18mg	0.18mg	22	69 years	31.82% Female
Metaproterenol 1.3mg	1.3mg	22	69 years	31.82% Female
Pirbuterol 0.4mg	0.4mg	22	69 years	31.82% Female
Terbutaline 0.4mg	0.4mg	22	69 years	31.82% Female

Outcomes:

Reporting of data is as follows:
Drug Name
n Baseline
n Follow-up
Mean Difference
Between Group Comparison

Efficacy Outcomes:

FEV1

Albuterol 0.18mg	Metaproterenol 1.3mg	Pirbuterol 0.4mg	Terbutaline 0.4mg
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
22 NR(NR)	22 NR(NR)	22 NR(NR)	22 NR(NR)
31.5(18.4)	27.0(16.4)	29.6(17.4)	28.5(14.2)

Notes: FEV measured at baseline and 30 mins after therapy. This process was repeated on an unspecified number of days (at least 5, but likely more depending on individual patients.) Results are presented as "final" although the duration of the study and the number of times each patient was challenged is not reported.

Other Efficacy/Effectiveness Outcomes and Comments:

Change in FEV1 as a percentage of predicted normal:
albuterol 10.3 (SD 5.2)
metaproterenol 8.7 (SD 4.9)
pibuterol 9.3 (SD 5.2)
terbutaline 8.6 (SD 4.0)

NR

Evidence Table 21. Pirbuterol vs terbutaline - Non-RCTs: safety only

Peacock, 1992 **Quality rating (Efficacy, Safety): Fair, NA**

Other Adverse Events and Comments:

NR

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Anani, 1989

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	6 (20	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	4 (13.3%)			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No, excluded 6 (20%)				
10. Postrandomization exclusions?	No				

Anderson, 1979

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	Unable to determine				

Asher, 1985

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Boehringer Ingelheim (NZ) Limited	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Berezuk, 1983

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: Univ of Arizona	
7. Care provider masked?	Yes				
8. Patients masked?	Yes			Comment: Data excluded for one patient due to unspecified protocol violation.	
9. Intention-to-treat analysis?	No, excluded 1 (9%)				
10. Postrandomization exclusions?	No				

Berkowitz, 1986

Design: RCT SB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Beumer, 1980; Beumer 1979

Design: RCT SB Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	Latin squar	11. Reporting of Attrition	Uncle	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	Unclear			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	Yes				
8. Patients masked?	Yes			Comment: No information about how many patients were initially randomized.	
9. Intention-to-treat analysis?	Unclear				
10. Postrandomization exclusions?	Unclear				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Blackhall, 1976	**Design:** RCT SB Parallel			**Trial type:** H2H		**Quality rating:** Fair		
1. Randomization adequate?	No	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528	
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR /	NR		
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	NR			
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica			
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No			
6. Outcome assessors masked?	NR			6. Funding: NR				
7. Care provider masked?	No							
8. Patients masked?	Yes							
9. Intention-to-treat analysis?	unclear							
10. Postrandomization exclusions?	Unable to determine							
Burgess, 1990	**Design:** RCT DB Crossover			**Trial type:** H2H		**Quality rating:** Fair		
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528	
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR /	NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR			
4. Eligibility criteria specified?	No	Contamination	No	4. Controlled group standard of care?	Not applica			
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No			
6. Outcome assessors masked?	Yes			6. Funding: NR				
7. Care provider masked?	Unclear, reported as double blind							
8. Patients masked?	Yes							
9. Intention-to-treat analysis?	Yes							
10. Postrandomization exclusions?	No							
Campbell, 1999; Campbell, 2000	**Design:** RCT Open Crossover			**Trial type:** H2H		**Quality rating:** Fair		
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528	
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR /	NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No			
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica			
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes			
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Astra Pharmaceuticals U.K. Ltd.				
7. Care provider masked?	Unclear, reported as double blind							
8. Patients masked?	No							
9. Intention-to-treat analysis?	No							
10. Postrandomization exclusions?	Yes							

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Capecchi, 1978

Design: RCT SB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Carl, 2003

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Good

1. Randomization adequate?	Yes	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Sepracor Inc.	
7. Care provider masked?	NR				
8. Patients masked?	Yes			Comment: 5 pts were excluded due to other chronic diseases	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Cazzola, 1994

Design: RCT SB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes for spirometric values;	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as single blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as single blind				
8. Patients masked?	Unclear, reported as single blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Cazzola, 1995	**Design:** RCT SB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No		
6. Outcome assessors masked?	No			6. Funding: NR			
7. Care provider masked?	NR						
8. Patients masked?	Yes						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						
Cazzola, 1998a	**Design:** RCT DB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No		
6. Outcome assessors masked?	Yes			6. Funding: NR			
7. Care provider masked?	NR						
8. Patients masked?	Yes						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						
Cazzola, 1998b	**Design:** RCT SB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No		
6. Outcome assessors masked?	No			6. Funding: NR			
7. Care provider masked?	NR						
8. Patients masked?	Yes						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Celik, 1999

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Chandra, 2004

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Good

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Chester, 1978

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	unclear	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	unclear
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: NR	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Chodosh, 1989 — Design: RCT DB Crossover — Trial type: H2H — Quality rating: Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	unclear
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	unclear
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: 3M Riker	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Unable to determine				

Choo-Kang, 1969 — Design: CT DB Crossover — Trial type: H2H — Quality rating: Fair

1. Randomization adequate?	Not random	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	NR				
10. Postrandomization exclusions?	Unable to determine				

Choo-Kang, 1973 — Design: RCT NR Crossover — Trial type: H2H — Quality rating: Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: Astra Chemicals Ltd., England	
7. Care provider masked?	NR				
8. Patients masked?	NR				
9. Intention-to-treat analysis?	No; excluded 8 (38%)				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Cockcroft, 1997

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Sepracor Inc,	
7. Care provider masked?	Yes				
8. Patients masked?	Yes			Comment: No demographic information given	
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Condemi, 2001

Design: RCT Open Parallel **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes;	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	No	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: Novartis Pharmaceutical Corporation, East Hanover, New Jersey.	
7. Care provider masked?	No				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Datta, 2003

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes			Comment: Attrition appears to be 0, but not explicitly stated	
9. Intention-to-treat analysis?	Unclear				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Dawson, 1985	**Design:** RCT DB Crossover			**Trial type:** H2H	**Quality rating:** Good
1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	No	3. Class naive patients only?	NR (likely not)
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	Yes				
8. Patients masked?	Yes, but not described				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				
Di Marco, 2003	**Design:** RCT DB Crossover			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				
Everden, 2002; Everden, 2004	**Design:** RCT Open Parallel			**Trial type:** H2H	**Quality rating:** Fair-poor
1. Randomization adequate?	Yes	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	Yes			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: Astra Zeneca, UK	
7. Care provider masked?	NR				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Francis, 1983

Design: RCT NR Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	NR				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Gawchik, 1999

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes 1	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	No placebo
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Sepracor Inc.	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	Yes				

Gioulekas, 1996

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes,	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	Yes			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No; excluded 7 (21.9%)				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Graff-Lonnevig, 1976

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	NR (likely no)
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	Unable to determine				

Gray, 1982

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Astra Pharmaceuticals; WB Pharmaceuticals	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Grembiale, 2005

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Grove, 1996 — Design: RCT SB Crossover — Trial type: H2H — Quality rating: Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	NR; o	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	Unclear			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Single blind; unclear who is blind; pro			6. Funding: NR	
7. Care provider masked?	Single blind; unclear who is blind; pro				
8. Patients masked?	Single blind; unclear who is blind; pro				
9. Intention-to-treat analysis?	Unclear; only gave no. of patients wh				
10. Postrandomization exclusions?	Unclear; only gave no. of patients wh				

Gumbhir-Shah, 1999 — Design: RCT DB Crossover — Trial type: H2H — Quality rating: Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	Yes	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR; affiliation of 1 author Sepracor Inc.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Handley, 2000 — Design: RCT DB Crossover — Trial type: H2H — Quality rating: Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Sepracor Inc.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Hanley, 1979 — Design: RCT NR NR — Trial type: H2H — Quality rating: Poor

1. Randomization adequate?	Method of r	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: W.B. Pharmaceuticals supplied the fenoterol and placebo aerosols.	
7. Care provider masked?	NR				
8. Patients masked?	Unclear, reported as blinded			Comment: Item #11: Yes; excluded patients whose baseline values at 24 hours differed by more than 10%	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Hardasmalani, 2005 — Design: RCT DB Parallel — Trial type: H2H — Quality rating: Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes, but not described			6. Funding: NR	
7. Care provider masked?	Yes, but not described				
8. Patients masked?	Yes			Comment: All patients compelted the study, but data only on 63/70; reason for loss NR	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Unable to determine				

Hockley, 1983 — Design: RCT DB Crossover — Trial type: H2H — Quality rating: Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	No	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: W.B. Pharmaceuticals	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Holt, 1983	**Design:** RCT Open Crossover			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				
Huhti, 1978	**Design:** RCT DB Crossover			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				
Hung, 2001	**Design:** RCT SB Parallel			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	No	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NR			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Konig, 1985

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Boehringer Ingelheim Ltd.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Unclear				
10. Postrandomization exclusions?	Unable to determine				

Kottakis, 2002

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Novartis Pharma AG (Basel, Switzerland)	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes			Comment: I patient excluded as didn't meet inclusion criteria, but included in per protocol analysis anyway	
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Lawford, 1987

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Method not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Only very minimal informati	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Lindsay, 1994

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	NR; o	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	NR			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: Author N.L. Russell associated with Astra Pharmaceuticals Pty. Ltd., Australia	
7. Care provider masked?	NR				
8. Patients masked?	No			Comment: Item #10: reported only # patients that took at least one dose and completed study	
9. Intention-to-treat analysis?	Unclear				
10. Postrandomization exclusions?	No				

Lipworth, 1995

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Boehringer Ingelheim (UK) Ltd	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Lopes dos Santos, 1991

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Lotvall J 2001

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	Yes	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	NA
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Glaxo Wellcome R&D Ltd.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Maesen, 1984

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Author P.J.G. Cornelissen affiliated with Boehringer Ingelheim BVV, Alkmaar, The Netherlands	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Malinen, 2000

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Good

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Orion Pharma, Finland	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Manicatide, 1978

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Ventolin, Bricanyl and Berotec were supplied by Allen & Hanburys Ltd., A.B. Draco and C.H. Boehringer Ingelheim, respectively	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Milgrom, 2001

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Sepracor Inc.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes			Comment: Withdrawals 19/398; including 6 for protocol violation	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Milner, 1971

Design: CT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	unclear
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Asthma Research Council	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	unclear				
10. Postrandomization exclusions?	Unable to determine				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity				External validity	
Munzenberger, 1989	**Design:** RCT NR Crossover			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				
Nelson, 1998; Pleskow, 2004	**Design:** RCT DB Parallel			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Sepracor Inc.	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				
Newhouse, 1994	**Design:** RCT DB Crossover			**Trial type:** H2H	**Quality rating:** Fair
1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Boehringer Ingelheim Canada Ltd.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Newhouse, 1996

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Good

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Boehringer Ingelheim (Canada) Ltd.	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Nightingale, 2002

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes;	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	Yes			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear			6. Funding: Novartis Pharmaceuticals	
7. Care provider masked?	NR				
8. Patients masked?	No			Comment: Item #7: blinded when on formoterol and placebo, but not salmeterol	
9. Intention-to-treat analysis?	No; excluded 10%				
10. Postrandomization exclusions?	No				

Nowak, 2004

Design: CT Open Parallel **Trial type:** H2H **Quality rating:** Fair, for cohort

1. Randomization adequate?	NA	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NA	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	
6. Outcome assessors masked?	No			6. Funding: Sepracor, In.	
7. Care provider masked?	No				
8. Patients masked?	No			Comment: Controlled clinical trial	
9. Intention-to-treat analysis?	NA				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Oldaeus, 1995

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	No			6. Funding: Author Elisabeth Stahl affiliated with Astra Draco AB, Clinical Research & Development	
7. Care provider masked?	NR				
8. Patients masked?	No				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Palmqvist, 1997

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: Astra Draco, Herman Krefting's Foundation for Asthma and Allergy Research	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Peacock, 1992

Design: CT Open Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not placebo
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	NR			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	NR			Comment: Bronchodilator survey (the results of which are analyzed separately here) was intended to act as a run-in for four-week trial, the results of which are not usable due to reporting method	
9. Intention-to-treat analysis?	No; excluded 4 (18.2%)				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Pedersen, 1985

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Pohunek, 2004

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Astra Zeneca	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes			Comment: 4 patients withdrawn: 2 for personal reasons, 2 for abnormal baseline ECG	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Qureshi, 2005

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	No	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Sepracor Inc.	
7. Care provider masked?	Yes				
8. Patients masked?	Yes			Comment: Per protocol analysis reported (6 patients excluded for protocol violation)	
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Ramsay, 1999	**Design:** RCT DB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes		
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Sepracor Inc.			
7. Care provider masked?	Unclear, reported as double blind						
8. Patients masked?	Unclear, reported as double blind						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						
Ribeiro, 1990	**Design:** RCT Open Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	Not random	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No		
6. Outcome assessors masked?	NA			6. Funding: AB Draco			
7. Care provider masked?	NA						
8. Patients masked?	NA						
9. Intention-to-treat analysis?	No						
10. Postrandomization exclusions?	Unable to determine						
Richter, 2002	**Design:** RCT DB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	593 /	528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No		
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Astra GmbH (Wedel, Germany)			
7. Care provider masked?	Unclear, reported as double blind						
8. Patients masked?	Unclear, reported as double blind						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Scalabrin, 1996

Design: RCT SB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	No	Adherence		3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	Yes, but not described				
9. Intention-to-treat analysis?	Unclear (likely yes)				
10. Postrandomization exclusions?	Unable to determine				

Schermer, 2004

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Novartis Pharma BV (Arnhem, The Netherlands)	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Skoner, 2005

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Unclear
5. Loss to follow-up, differential?	Yes			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Sepracor, Inc	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes			Comment: Analyses based on "ITT" population. For safety, this is clearly stated as being 211 pts. For efficacy/effectiveness, no actual number of patients is specified, so unclear if truly ITT.	
9. Intention-to-treat analysis?	Unclear				
10. Postrandomization exclusions?	Unable to determine				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Sturani, 1983

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Yes
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	Yes				
8. Patients masked?	Yes			Comment: Graphical data only; States that "12 patients were studied"; unclear if any attrition	
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Tandon, 1980

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	NA			6. Funding: NR	
7. Care provider masked?	NA				
8. Patients masked?	NA				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?					

Tang, 1984

Design: RCT SB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Method not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Method not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	NR
4. Eligibility criteria specified?	No	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: W.B. Pharmaceuticals	
7. Care provider masked?	No				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Tinkelman, 1990

Design: RCT DB Parallel **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes, but not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Riker Laboratories, Inc.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Unable to determine				

Towns, 1983

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: Astra Pharmaceuticals; Glaxo Australia.	
7. Care provider masked?	NR				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Trembath, 1979

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Not random	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	Yes, but not described	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: W.B. Pharmaceuticals	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

van Noord, 1996	**Design:** RCT DB Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes		
6. Outcome assessors masked?	Yes			6. Funding: NR			
7. Care provider masked?	NR						
8. Patients masked?	Yes						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						
Verini, 1998	**Design:** RCT NR Crossover			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	NR	3. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	Not applica		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes		
6. Outcome assessors masked?	No			6. Funding: NR			
7. Care provider masked?	No						
8. Patients masked?	No						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						
Vervloet, 1998; Rutten-van Molken, 199	**Design:** RCT Open Parallel			**Trial type:** H2H		**Quality rating:** Fair	
1. Randomization adequate?	NR	11. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528		
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR		
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Yes		
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes		
6. Outcome assessors masked?	No			6. Funding: Novartis Pharmaceuticals			
7. Care provider masked?	No						
8. Patients masked?	No						
9. Intention-to-treat analysis?	Yes						
10. Postrandomization exclusions?	No						

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Vilsvik, 1991

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Poor

1. Randomization adequate?	NR	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	No	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Author Stig Holthe affiliated with Astra Farmasoytiske A/S	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	No				
10. Postrandomization exclusions?	Yes				

Vilsvik, 1993

Design: RCT Open Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	Yes;	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	No placebo
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	No			6. Funding: NR	
7. Care provider masked?	No				
8. Patients masked?	No				
9. Intention-to-treat analysis?	No; excluded 12 (7%)				
10. Postrandomization exclusions?	No				

Volkl, 1991

Design: RCT NR Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	NR	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	NR	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	No placebo
5. Loss to follow-up, differential?	NR			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	NR, but suspect open study			6. Funding: NR	
7. Care provider masked?	NR, but suspect open study				
8. Patients masked?	NR, but suspect open study				
9. Intention-to-treat analysis?	NR				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity **External validity**

Webb, 1982

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	11. Reporting of Attrition	NR	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	Nr	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	No placebo
5. Loss to follow-up, differential?	NR			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: Astra Laboratories	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Windom, 1990

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Yes	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Yes			6. Funding: Medical Research Council of New Zealand; the Asthma Foundation of New Zealand.	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	Unable to determine				

Wong, 1990

Design: RCT DB Crossover **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	Method not	11. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover		2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence		3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination		4. Controlled group standard of care?	Not applica
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	No
6. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR	
7. Care provider masked?	Unclear, reported as double blind				
8. Patients masked?	Unclear, reported as double blind				
9. Intention-to-treat analysis?	Yes				
10. Postrandomization exclusions?	No				

Evidence Table 22. Quality assessment of efficacy trials

Internal validity				External validity	
Yang, 1996	**Design:** RCT DB Crossover			**Trial type:** H2H	**Quality rating:** Fair-Poor
1. Randomization adequate?	NR	11. Reporting of Attrition	Yes;	1. Number Screened/ Eligible/ Enrolled:	NR / 593 / 528
2. Allocation adequate?	NR	Crossover	NR	2. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	NR	Adherence	NR	3. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	NR	4. Controlled group standard of care?	No placebo
5. Loss to follow-up, differential?	No			5. Exclusion criteria reported?	Yes
6. Outcome assessors masked?	Yes			6. Funding: NR	
7. Care provider masked?	Yes				
8. Patients masked?	Yes				
9. Intention-to-treat analysis?	No; 5 (27.8%) excluded				
10. Postrandomization exclusions?	No				

Evidence Table 23. Quality assessment of safety trials

Anani, 1989	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Anderson, 1979	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Berezuk, 1983	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	NR
Comments	

Evidence Table 23. Quality assessment of safety trials

Beumer, 1980; Beumer 1979	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	No
Comments	

Blackhall, 1976	**Design:** RCT SB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Burgess, 1990	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Campbell, 1999; Campbell, 2000	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Capecchi, 1978	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Carl, 2003	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Carmichael, 1980	**Design:** CT DB NR	**Trial type:** H2H	**Quality rating:** Fair/poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Cazzola, 1994	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	No
Comments	

Cazzola, 1998a	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	No
Comments	

Evidence Table 23. Quality assessment of safety trials

Cazzola, 1998b	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	No
Comments	

Celik, 1999	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Chandra, 2004	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Chodosh, 1989	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	unclear
Comments	

Choo-Kang, 1969	**Design:** CT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	
Comments	

Choo-Kang, 1973	**Design:** RCT NR Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	No
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Condemi, 2001	**Design:** RCT Open Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Datta, 2003	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Dawson, 1985	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Eryonucu, 2001	**Design:** RCT NR Crossover	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Not clear
Comments	

Eryonucu, 2005	**Design:** RCT NR Parallel	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	NR
Comments	

Everden, 2002; Everden, 2004	**Design:** RCT Open Parallel	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	No
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Freisleben, 1971	**Design:** CT NR NR	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	NR
2. Low overall loss to follow-up?	NR
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	NR
Comments	

Garrett, 1996	**Design:** Cohort NR NR	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	NA
2. Low overall loss to follow-up?	NA
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Yes
Comments	Confounders were carefully considered. Follow-up adequate

Gawchik, 1999	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Gioulekas, 1996	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	No
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Graff-Lonnevig, 1976	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Gray, 1982	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Grembiale, 2005	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Grove, 1996	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	NR
Comments	

Gumbhir-Shah, 1999	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Handley, 2000	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Hockley, 1983	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	NA
Comments	

Holt, 1983	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Huhti, 1978	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Hung, 2001	**Design:** RCT SB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Konig, 1985	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Kottakis, 2002	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Lin, 2002	**Design:** RCT NR NR	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Lindsay, 1994	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Lipworth, 1995	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Lotvall J 2001	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Maesen, 1984	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Malinen, 2000	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Not clear
Comments	

Manicatide, 1978	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Milgrom, 2001	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Milner, 1971	**Design:** CT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear, a
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	f/u unclear
Comments	

Munzenberger, 1989	**Design:** RCT NR Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Nelson, 1998; Pleskow, 2004	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Newhouse, 1994	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair/poor

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Newhouse, 1996	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Nightingale, 2002	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	No
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Nowak, 2004	**Design:** CT Open Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Oldaeus, 1995	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Palmqvist, 1997	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Pohunek, 2004	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	no
Comments	

Qureshi, 2005	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Yes
Comments	

Ribeiro, 1990	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	
Comments	

Evidence Table 23. Quality assessment of safety trials

Roth, 1977	**Design:** CT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Not clear
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	
Comments	

Scalabrin, 1996	**Design:** RCT SB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Skoner, 2005	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Spitzer, 1992	**Design:** Cohort NA NR	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Yes
Comments	

Suissa, 1994	**Design:** Cohort NA NA	**Trial type:** H2H	**Quality rating:** Good

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	NA
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	Yes
7. Adequate duration of follow-up?	Yes
Comments	

Tammivaara, 1979	**Design:** RCT NR NR	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	NR
2. Low overall loss to follow-up?	NR
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	NR
Comments	

Evidence Table 23. Quality assessment of safety trials

Tandon, 1980	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair/Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Tang, 1984	**Design:** RCT SB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	Method of AE ascertainment unclear for tremor only - appears to be self-report

Tinkelman, 1990	**Design:** RCT DB Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Towns, 1983	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Trembath, 1979	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	No
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	
Comments	

van Noord, 1996	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Vervloet, 1998; Rutten-van Molken, 199	**Design:** RCT Open Parallel	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Vilsvik, 1991	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Unclear
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Vilsvik, 1993	**Design:** RCT Open Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Evidence Table 23. Quality assessment of safety trials

Volkl, 1991	**Design:** RCT NR Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Yes
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Not clear
6. Statistical analysis of potential confounders?	Not clear
7. Adequate duration of follow-up?	
Comments	

Webb, 1982	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Poor

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	No
4. Ascertainment techniques adequately described?	No
5. Non-biased and adequate ascertainment methods?	Self report
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Not clear
Comments	

Windom, 1990	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair

1. Non-biased selection?	Not clear
2. Low overall loss to follow-up?	Yes
3. Adverse events pre-specified and defined?	Yes
4. Ascertainment techniques adequately described?	Yes
5. Non-biased and adequate ascertainment methods?	Yes
6. Statistical analysis of potential confounders?	No
7. Adequate duration of follow-up?	Yes
Comments	

Evidence Table 23. Quality assessment of safety trials

Wong, 1990	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Good
1. Non-biased selection?	Not clear		
2. Low overall loss to follow-up?	Yes		
3. Adverse events pre-specified and defined?	Yes		
4. Ascertainment techniques adequately described?	Yes		
5. Non-biased and adequate ascertainment methods?	Yes		
6. Statistical analysis of potential confounders?	No		
7. Adequate duration of follow-up?	Yes		
Comments			

Yang, 1996	**Design:** RCT DB Crossover	**Trial type:** H2H	**Quality rating:** Fair
1. Non-biased selection?	Not clear		
2. Low overall loss to follow-up?	Yes		
3. Adverse events pre-specified and defined?	Yes		
4. Ascertainment techniques adequately described?	Yes		
5. Non-biased and adequate ascertainment methods?	Yes		
6. Statistical analysis of potential confounders?	No		
7. Adequate duration of follow-up?	Not clear		
Comments			