

## **Online Supplementary Material**

### **LABAs plus Inhaled Corticosteroids safety: a systematic review of non-randomized studies**

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**eMethods1 . Search Strategy**

**MEDLINE**

((asthma[MeSH Terms]) OR asthma\*[Text Word]) AND (((adrenergic beta 2 agonists[MeSH Terms]) OR long acting\*[Text Word]) OR long-acting\*[Text Word]) OR LABA\*[Text Word]) OR salmeterol[Text Word] OR formoterol[Text Word] ) NOT clinical trials, randomized[MeSH Terms].

**EMBASE**

('asthma'/exp OR asthma AND [humans]/lim AND [2000-2012]/py) AND ('beta 2 adrenergic receptor stimulating agent'/exp OR 'formoterol'/exp OR 'salmeterol'/exp OR (laba AND [2000-2012]/py))

**eTable I. Study Inclusion and Exclusion Criteria**

<b>PICO criteria</b>	<b>Inclusion and exclusion criteria</b>
<b>Population and condition of interest</b>	<p>Study design included in one of these: non-randomized controlled trials, controlled before-after studies; prospective cohort studies, retrospective cohort studies, historically controlled trials, case-control studies and nested case-control studies.</p> <p>Studies that enrolled patients with asthma diagnosed.</p> <p>Studies included adults, children and mixed age population (adult and children)</p>
<b>Interventions</b>	All studies included LABAs combined with ICs (single or separate inhalers)
<b>Comparator</b>	ICs alone (co-medication was admitted such as SABA, immunomodulators)
<b>Outcomes</b>	We included studies that reported the following outcomes: severe exacerbation (use of systemic corticosteroids, asthma-related emergency room visits, hospitalizations, intubations, or intensive care unit admissions), moderate exacerbation (use of SABA) , adverse events, death

**eTablell: Risk of bias assessment Cochrane´s Checklist****Item**

**Was there a comparison between 2 or more groups of participants receiving different interventions?**

**Were participants allocated to groups:**

- by treatment decisions?
- by participant's preferences?
- on the basis of outcome?

**Which part of the study was prospective?**

- Identification of participants\*
- Assessment of baseline and allocation to intervention?\*
- Assessment of outcomes?
- Assessment of hypothesis?

**On what variables was comparability between groups assessed?**

- Potential confounders?
- Baseline assessment of outcome variables?

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***\*only for Prospective Studies***

**Options: YES / No / Possibly**

**eTable III: Reasons for exclusion in each step of the Systematic Review**

<b>MEDLINE</b>	<b>Review of titles</b>	<b>Review of abstracts</b>	<b>Review of manuscripts</b>
<b>1. Inclusion (eligible for next review step)</b>			
<b>2. Study design</b>			
2a. Randomized clinical trial	116 (8.1%)	429 (34.4%)	22 (14.2%)
2b. Ecological	1 (0.1%)	2 (0.2%)	1 (0.6%)
2c. Health economic evaluations	37 (2.6%)	20 (1.6%)	1 (0.6%)
2d. Systematic Review / Meta-analysis	51 (3.6%)	30 (2.4%)	
2e. Pooled		2 (0.2%)	2 (1.3%)
2x. Others	7 (0.5%)	27 (2.2%)	31 (20%)
<b>3. Population</b>			
3a. COPD	79 (5.5%)	4 (0.3%)	1 (0.6%)
3X. Others	52 (3.6%)	15 (1.2%)	3 (0.6%)
<b>4. Treatment</b>			
4a. SABAs	20 (1.4%)	3 (0.2%)	3 (1.9%)
4b. Omalizumab / Lebrikizumab	34 (2.4%)	3 (0.2%)	1 (0.6%)
4c. Antileukotriens: Montelukast/Pranlukast	51 (3.6%)	2 (0.2%)	5 (3.2%)
4d. Bronchial thermoplasty		2 (0.2%)	
4X. Others	91 (6.4%)	14 (1.1%)	46 (29.7%)
<b>5. Administration Form</b>			
5a. Oral	7 (0.5%)	1 (0.1%)	
5X. Others	4 (0.3%)		
<b>6. Publication type</b>			
6a. Reviews	238 (16.6%)	546 (43.7%)	2 (1.3%)

6b. Case series / case report	22 (1.5%)	8 (0.6%)	2 (1.3%)
6c. Letter to the editor	22 (1.5%)	1 (0.1%)	
6d. Comments	71 (5.0%)	18 (1.4%)	
6e. Guidelines	29 (2.0%)	1 (0.1%)	
6X. Others	8 (0.6%)	4 (0.3%)	
<b>7. Outcome</b>			
7c. HRQL and other PRO	14 (1.0%)	14 (1.1%)	2 (1.3%)
7X. Others	50 (3.5%)	50 (4.0%)	29 (18.7%)
<b>8. Others</b>			
8a. Pathophysiology and medication	257 (18.0%)	18 (1.4%)	3 (1.9%)
8b. No thumans	11 (0.8%)	2 (0.2%)	3 (1.9%)
8c. Genetics	71 (5.0%)	1 (0.1%)	
8d. Diagnostic	59 (4.1%)		
8X. Others	28 (2.0%)	29 (2.3%)	
<b>TOTAL</b>	<b>1430</b>	<b>1246</b>	<b>155</b>

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<b>EMBASE</b>	<b>Review of titles</b>	<b>Review of abstracts</b>	<b>Review of manuscripts</b>
<b>1. Inclusion (eligible for next review step)</b>			
<b>2. Study design</b>			
2a. Randomized clinical trial	12 (1.2%)	10 (3.4%)	
2b. Ecological		2 (0.7%)	
2c. Health economic evaluations	14 (1.4%)	11 (3.7%)	
2d. Systematic Review / Meta-analysis	10 (0.1%)	3 (1%)	
2e. Pooled			
2x. Others	1 (0.01%)	18 (6.1%)	1 (3.3%)
<b>3. Population</b>			
3a. COPD	50 (4.8%)	3 (1%)	
3b. Rhinitis	6 (0.6%)		
3c. Allergy	15 (1.5%)	1 (0.3%)	
3X. Others	188 (18.2%)	1 (0.3%)	
<b>4. Treatment</b>			
4a. SABAs	9 (0.9%)	5 (1.7%)	
4b. Omalizumab / Lebrikizumab	44 (4.3%)	4 (1.4%)	1 (3.3%)
4c. Antileukotriens: Montelukast / Pranlukast	55 (5.3%)	4 (1.4%)	
4d. Bronchial thermoplasty	5 (0.5%)		
4e. Anticholinergics	1 (0.1%)		
4X. Others	102 (9.9%)	31 (10.5%)	2 (6.7%)
<b>5. Administration Form</b>			
5a. Oral	1 (0.1%)		
5b. IV	1 (0.1%)		

5X. Others	5 (0.5%)		
<b>6. Publication type</b>			
6a. Reviews	33 (3.2%)	56 (19%)	
6b. Case series / case report	135 (13.1%)	12 (4.1%)	
6c. Letter to the editor	6 (0.6%)		
6d. Comments	19 (1.8%)	1 (0.3%)	
6e. Guidelines	18 (1.7%)		
6X. Others	8 (0.8%)		13 (43.3%)
<b>7. Outcome</b>			
7a. Congenital malformation	8 (0.8%)		
7c. HRQL and other PRO	17 (1.6%)	4 (1.4%)	
7X. Others	73 (7.1%)	109 (37.1%)	5 (16.7%)
<b>8. Others</b>			
8a. Pathophysiology and medication	31 (3%)	2 (0.7%)	
8b. Not humans	1 (0.1%)		
8c. Genetics	65 (6.3%)	2 (0.7%)	
8d. Diagnostic	40 (3.9%)		
8X. Others	58 (5.6%)	15 (5.1%)	2 (6.7%)
<b>9. Repeated</b>			6 (20%)
<b>TOTAL</b>	1031	294	30

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**eTableIV: Characteristics of excluded studies**

Author	Study characteristics			Type of inhaler	Reason for exclusion	Outcomes
	Study type	Population (N)	Age (Range)			
Elkout et al.2012	RC	3172	0-18	Sin & Sep	Other outcome	Number of SABA and courses of SysCort prescribed annually.
Navaratnam et al.2011	RC	16063	12-65	Single	No LABA in intervention group	Asthma control outcomes
Butland et al. 2011	C-C	1064	1-64	Not stated	Exposure not divided in adequate groups	Asthma deaths
Liao et al.2010	PC	2236	12-54	Not stated	Other outcome	Risk of admission among ED patients with Acute Asthma
Elkout et al. 2010	RC	10454	0-18	Sin & Sep	Comparison IC/LABA vs IC+LABA	Number of SABA prescription, prescription of systemic corticosteroid use
Zhang et al.2009	RC	507966	> 18	Not stated	Other outcome	Acute myocardial infarction
Smith et al. 2009	RC	3013	5-62	Sin & Sep	Outcome not related to medication	Exacerbation requiring hospital visit
Plaza et al.2009	RC	1153	15-69	Not stated	Descriptive analysis of clinical characteristics of asthma exacerbations	Clinical characteristics: mortality, length of stay, gas exchange, lung function.
Navaratnam et al.2009	RC	8188	12-65	Single	No endpoint measure	Mean of exacerbations
Spahn et al.2009	RC	46774	4-55	Single	Comparison group not stated	Asthma-related ED visits and hospitalization

Wang et al.2008	C-C	1940	> 5	Not stated	Exposure not divided in adequate groups	Asthma-related hospitalization
Borderias et al.2007	RC	696	15-55	Not stated	Addition of Montelukast to IC plus LABA treatment	Asthma attacks, use of SABAs
Lyell et al.2005	CC	105	<16	Not stated	Exposure not divided in adequate groups	Factors that may predict severe asthma attacks
Laforest et al.2005	RC	1038	17-50	Not stated	Other outcome	Antibiotic prescription
Angus et al. 2005	RC	588	4-55	Sin & Sep	Comparison IC/LABA vs IC+LABA	SABA use, Oral corticosteroids use
Anderson et al. 2005	C-C	1064	< 65	Not stated	Exposure not divided in adequate groups	Asthma deaths
Chan et al. 2004	RC	2246	12-55	Sin & Sep	Comparison IC/LABA vs IC+LABA	Asthma-related ED visits, asthma-related hospitalization, use of SABA, systemic corticosteroid use

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**RC:** Retrospective Cohort; **C-C:** case-control study; **PC:** Prospective cohort; **BS:** Before-after study; **Sing & Sep:** Single and separate inhalers; **HR=** Hazard Ratio; **OR=**Odds Ratio; **a=**adjusted; **u=**unadjusted; ED = Emergency Room; **PS=** Propensity Score

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