EFFECT OF ANTI-INFLAMMATORY ASTHMA MEDICATION ON FENO VALUES ï A META-ANALYSIS

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ABSTRACT

INTRODUCTION: Asthma is a chronic inflammatory disorder of the airways. FENO values are currently used to diagnose, monitor and treat asthma. There are no studies summarizing the effects of the various anti-inflammatory drugs on FENO values. AIM: The aim of this study is to determine the effect of the different anti-inflammatory asthma medications on FENO values. METHODS: A systematic review was made of published studies on the effects of Corticosteroids and Leukotriene Antagonists on FENO values and a Meta-analysis was conducted to determine the magnitude of those effects. RESULTS: 53 articles were included in our study and 62 interventions were separately analyzed. All reported lower FENO values following anti-inflammatory treatment. Flunisolide produced a reduction of -23.50ppb [-27.0 to -20.0]. Beclomethasone, Fluticasone, Budesonide and Prednisone caused decreases of -18.73ppb [-29.06 to -8.41]; -17.19ppb [-23.55 to -10.84]; -15.56ppb [-20.61 to -10.52]; and -11.39ppb [-17.37 to -5.41], respectively and Montelukast lowered FENO values by -10.18ppb [-13.50 to -6.86]. DISCUSSION: All of the anti-inflammatory drugs studied decrease FENO values, although many factors are involved.

KEY-WORDS: *Asthma, nitric oxide, leukotrienes antagonists, corticosteroids*

INTRODUCTION

Asthma is one of the most common chronic diseases, affecting 300 million people worldwide [1]. In recent years, exhaled Nitric Oxide (NO) testing has been used to diagnose, monitor and treat asthma. As NO is a gas produced by the cells of the airways in response to inflammatory processes, it can be used as an indicator of the cellsôinflammation and, consequently, can be used to diagnose and monitor chronic inflammatory diseases like asthma. In fact, the fraction of NO present in exhaled air (FENO), measured by an easy, reproducible, non-invasive and widely-accepted test, is currently being used to assess the effectiveness of anti-inflammatory treatment and, hence, guide the treatment of asthma [2-7].

The different types of asthma medication can be classified in two groups, according to their function: Anti-inflammatory Agents (Leukotriene Antagonists and Corticosteroids) and Airway Openers (ß2-Agonists).

Leukotrienes are substances released by mast stem cells, which are thought to cause allergy and asthma symptoms; they are the main reason for bronchoconstriction during an asthma attack [8]. Leukotriene Antagonists block the effects of these substances and prevent their release.

Corticosteroids affect the immune system in various ways to prevent inflammation of the airways. They have been shown to decrease the production of cytokines, which generate the inflammatory response, and are therefore used to treat asthma relapse [9].

The data suggest that anti-inflammatory agents influence FENO values although many biological factors, such as age, sex or atopy, also cause FENO variations [10].

As there are no studies summarizing the effects of the various anti-inflammatory drugs (Table 1) on FENO values, our aim was to perform a meta-analysis of the literature to quantify the effect on FENO values of the various anti-inflammatory asthma medications.

METHODS

Study Design

A systematic review and a meta-analysis was made of published studies of the effects of anti-inflammatory asthma medication (Table 1) on FENO values. The study design is summarized in Appendix 1.

Table 1 ï List of drugs for each class of anti-inflammatory asthma treatment

Anti-inflammatory Agent	Drugs
Leukotriene Antagonists	Montelukast Zafirlukast Zileuton
Inhaled Corticosteroids	Fluticasone Budesonide Triamcinolone Flunisolide Beclomethasone Mometasone
Oral Corticosteroids	Prednisone Methylprednisolone Hydrocortisone

Data Source

A computerized literature search was performed, using MEDLINE, ISI Web of Knowledge and Scopus databases, to obtain articles in which the topic or data considered the effect of anti-inflammatory medication on FENO values. A sensitive and specific query was built and applied for each database (Appendix 2). The results obtained in each case were then combined.

Study Selection

The articles were selected in two stages. The first considered the title and abstract, while the second analyzed the full text. In both stages the articles were randomly distributed and reviewed independently by two reviewers using inclusion and exclusion criteria (Table 2). Articles repeated in more than one data base were identified in the first stage. Reviewersôopinions were compared for each article; if they disagreed at the first stage, the article was automatically included in the second stage. The same process was used in the latter, but disagreements were resolved by a third reviewer.

Table 2 : Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
- Explicit comparison of FENO values in patients treated with anti-inflammatory medication with the values, in the same group of patients not on treatment; **- Related to the effects of Oral Corticosteroids, Inhaled Corticosteroids or Leukotriene modifiers on FENO values;** **- Experimental longitudinal study;** **- Primary data;** **- Published since 1990.**	**- In a language other than English, Portuguese or Spanish;** **-Studies without a rigorous definition about the existence or not of asthma in the patients, at the beginning of the treatment;** **- Participants other than humans.**

Quality Assessment

In the quality assessment stage, we aim to include only articles which have a high credibility rating, in order to prevent the inclusion of unreliable data that could change the final results. Articles which did not satisfy at least one of the following criteria (Table 3) were excluded.

Table 3: Quality Assessment Criteria used in the Quality Assessment Stage

Were subjects randomized?
Were patients analyzed in the groups to which they were randomly distributed?
Was the follow up complete?
Was the number of patients enough to trust the results?
Were the data presented in a way that allows extraction?
Were the treatment characteristics specified?

Data Extraction

A data extraction form was created with descriptive variables and the treatment applied to patients ï FENO values with and without treatment (Appendix 3).

FENO values were extracted in ppb, and the Standard Deviation was extracted or calculated using Confidence Intervals.

$$CI=+/-[mean+[2*(standard\ deviation)]/\sqrt{(number\ of\ patients)}]$$

Statistical Analysis and Synthesis of Study Results (meta-analysis)

Statistical Analysis and database construction were performed using SPSS [11]. The absolute and relative frequencies (%) of the studiesôcharacteristics were measured.

Review Manager 5.0 [12] was used to perform meta-analysis. Forest plots were created, heterogeneity between the studies was assessed, and the effect of each anti-inflammatory asthma treatment on FENO values, and respective 95% CI, was calculated.

RESULTS

Research and Assessment Results

The database search produced 315 studies. From these, following all the assessment stages, 53 [13-65] articles were selected for our Systematic Review (Fig. A; Table 4).

1 ï Title and Abstract Assessment; 2 ï Full Text Assessment; 3 ï Quality Assessment

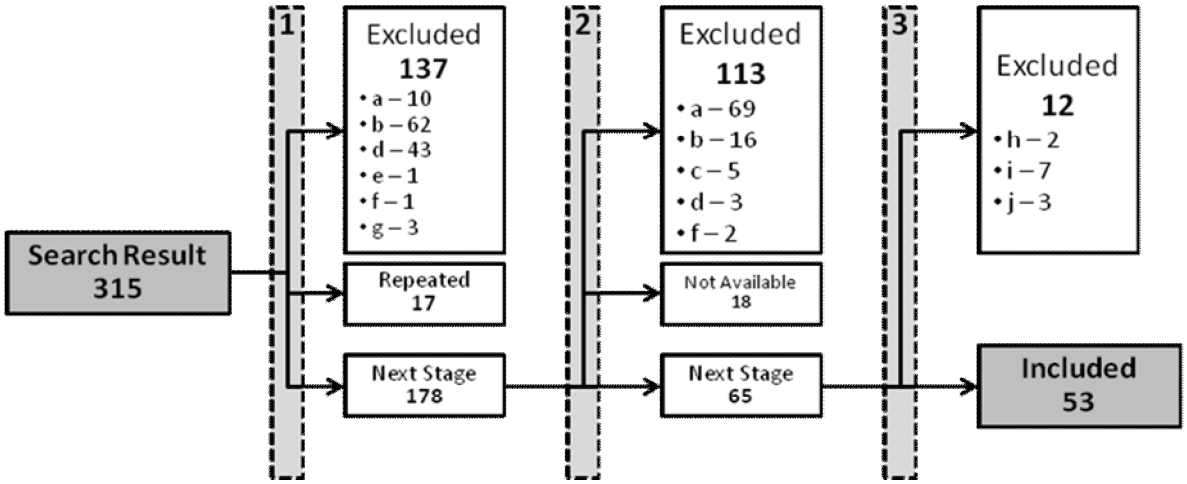


Fig. A: Flow diagram presenting the Assessmentôs Results

a - Doesn't study the effects on the same group of patients with and without the treatment;
b - Not related to the effects of anti-inflammatory treatment on FENO values;
c - Not experimental longitudinal studies;
d - Not primary data;
e - Not in English, Portuguese or Spanish;
f - No clear definition about the health condition of the patients;
g - Patients other than humans;
h - Insufficient number of patients;
i - Data not presented in a way that allows extraction;
j - Treatment characteristics not specified

Description of the included articles

We were unable to find studies on all of the anti-inflammatory asthma treatments. Only one study dealt with Flunisolide treatment.

From the 53 studies included, 8 considered more than one intervention. In these cases, we extracted data from each intervention as if they were separate studies. One study, Wilson2000[44], reports on 3 different interventions, so it was triplicated. A total of 62 interventions were studied (Table 5).

Table 4: Identification of Included studies; (2) by Author and Publication Year

Code	Title of the Article
Hung2005[13]	Discrepant clinical responses and blood chemokine profiles between two non-steroidal anti-inflammatory medications for children with mild persistent asthma.
Montuschi2006[14]	Effects of a leukotriene receptor antagonist on exhaled leukotriene E4 and prostanoids in children with asthma.
Bonsignore2008[15]	Effects of exercise training and montelukast in children with mild asthma.
Moeller2008[16]	Effects of montelukast on subjective and objective outcome measures in preschool asthmatic children.
Lee2005[17]	Effects of montelukast on symptoms and eNO in children with mild to moderate asthma.
Montuschi2007[18]	Effects of montelukast treatment and withdrawal on fractional exhaled nitric oxide and lung function in children with asthma.
Bratton1999[19]	Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: a preliminary study.
Hung2007[20]	Montelukast decreased exhaled nitric oxide in children with perennial allergic rhinitis.
Bisgaard1999[21]	NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast.
Hung2007(2)[22]	Regulation of stromal cell-derived factor-1 and exhaled nitric oxide in asthmatic children following montelukast and ketotifen treatment.
Zeiger2007[23]	Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma.
Chuang2007[24]	Suppression of plasma matrix metalloproteinase-9 following montelukast treatment in childhood asthma.
Berkman2003[25]	The effect of montelukast on bronchial provocation tests and exhaled nitric oxide levels in asthmatic patients.
Straub2005[26]	The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old.
Straub2005(2)[27]	The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma.
Lee2005(2)[28]	Airway and systemic effects of hydrofluoroalkane formulations of high-dose ciclesonide and fluticasone in moderate persistent asthma.
Fujimoto2006[29]	Characteristics of asthma resistant to moderate dose inhaled corticosteroid treatment on bronchial hyperresponsiveness.
Lee2003[30]	Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma.
Reddel2008[31]	Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomised controlled trial.
Zietko2006[32]	Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma.
Rensen1999[33]	Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma.
Currie2003[34]	Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients.
Kelly2006[35]	Eosinophilic bronchitis in asthma: a model for establishing dose-response and relative potency of inhaled corticosteroids.
Loppow2001[36]	In patients with chronic bronchitis a four week trial with inhaled steroids does not attenuate airway inflammation.
Li2006[37]	Once-daily fluticasone propionate in stable asthma: study on airway inflammation.
Fritscher2009[38]	The effect of montelukast on exhaled nitric oxide of alveolar and bronchial origin in inhaled corticosteroid-treated asthma.
Jatakanon1998[39]	An inhaled steroid improves markers of airway inflammation in patients with mild asthma.
DalNegro2003[40]	Assessment of inhaled BDP-dose dependency of exhaled nitric oxide and local and serum eosinophilic markers in steroids-naive nonatopic asthmatics.
Carrà2001[41]	Budesonide but not nedocromil sodium reduces exhaled nitric oxide levels in asthmatic children
Beck-Ripp2002[42]	Changes of exhaled nitric oxide during steroid treatment of childhood asthma.
Kharitonov2002[43]	Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma.
Wilson2000[44]	Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma.
Silkoff2001[45]	Dose-response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients.
Lim1999[46]	Effect of inhaled budesonide on lung function and airway inflammation. Assessment by various inflammatory markers in mild asthma.
Kannie2001[47]	Effect of inhaled ciclesonide on airway responsiveness to inhaled AMP, the composition of induced sputum and exhaled nitric oxide in patients with mild asthma.
Pijnenburg2005[48]	Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission.
Haahtela2006[49]	Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study.
Miraglia2007[50]	Formoterol, montelukast, and budesonide in asthmatic children: effect on lung function and exhaled nitric oxide.
Covar2003[51]	Relations between exhaled nitric oxide and measures of disease activity among children with mild-to-moderate asthma.
Bodini2006[52]	Flunisolide decreases exhaled nitric oxide and nitrotyrosine levels in asthmatic children.
Lanz1999[53]	Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticoids in children.
Ghiro2003[54]	Effect of montelukast added to inhaled corticosteroids on fractional exhaled nitric oxide in asthmatic children.
Baraldi1998[55]	Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study.
Silkoff1998[56]	Exhaled nitric oxide and bronchial reactivity during and after inhaled beclomethasone in mild asthma.
Ferreira2001[57]	Exhaled nitric oxide and hydrogen peroxide in patients with chronic obstructive pulmonary disease: effects of inhaled beclomethasone.
Zietkowski2005[58]	The influence of inhaled corticosteroids on exhaled nitric oxide in stable chronic obstructive pulmonary disease.
Downie2007[59]	Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation.
Gelb2004[60]	Alveolar and airway sites of nitric oxide inflammation in treated asthma.
Payne2001[61]	Evidence for different subgroups of difficult asthma in children.
Szefler2002[62]	Exhaled carbon monoxide levels after a course of oral prednisone in children with asthma exacerbation.
Baraldi1999[63]	Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children.
Slats2006[64]	Improvement in bronchodilation following deep inspiration after a course of high-dose oral prednisone in asthma.
Payne2001(2)[65]	Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone.

Table 5: Interventions Description; (2) by author and year of publication (b and c distinguish between different interventions considered in the same study)

Study	n Patients	Age Group	Health Condition	Smoker
MONTELUKAST				
Hung2005	37	Children	Asthmatic	Not reported
Montuschi2006	17	Children	Asthmatic+Atopic	Not reported
Bonsignore2008	25	Children	Asthmatic	Not reported
Moeller2008	12	Children	Asthmatic	Non smoking
Lee2005	20	Children	Asthmatic	Not reported
Montuschi2007	14	Children	Asthmatic	Not reported
Bratton1999	12	Children	Asthmatic	Not reported
Hung2007	11	Children	Asthmatic	Not reported
Bisgaard1999	26	Children	Asthmatic	Not reported
Hung2007(2)	20	Children	Asthmatic	Not reported
Zeiger2007b	127	Children	Asthmatic	Not reported
Chuang2007	13	Children	Asthmatic	Not reported
Berkman2003	19	Mixed	Asthmatic	Not reported
Straub2005	30	Children	Asthmatic+Atopic	Non smoking
Straub2005(2)	24	Children	Asthmatic	Non smoking
FLUTISONE				
Lee2005(2)	14	Adults	Asthmatic	Non smoking
Fujimoto2006	34	Adults	Asthmatic	Mixed
Lee2003b	29	Adults	Asthmatic	Non smoking
Reddel2008	23	Adults	Asthmatic+Atopic	Mixed
Zietkowski2006	11	Adults	Asthmatic	Non smoking
Rensen1999	12	Adults	Asthmatic	Not smoker
Currie2003	15	Adults	Asthmatic	Not reported
Kelly2006	14	Adults	Asthmatic	Not smoker
Loppow2001	19	Adults	Bronquitis	Mixed
Li2006	29	Children	Asthmatic	Not reported
Zeiger2007a	127	Children	Asthmatic	Not reported
Fritscher2009	18	Adults	Asthmatic	Non smoking
BUDESONIDE				
Jatakanon1998	5	Adults	Asthmatic+Atopic	Non smoking
DalNegro2003a	10	Adults	Asthmatic	Not reported
DalNegro2003b	10	Adults	Asthmatic	Not reported
Carrà2001	11	Children	Asthmatic	Not reported
Beck-Ripp2002	54	Children	Asthmatic	Not reported
Lee2003a	29	Adults	Asthmatic	Non smoking
Kharitonov2002a	26	Adults	Asthmatic	Not reported
Kharitonov2002b	26	Adults	Asthmatic	Not reported
Wilson2000a	26	Adults	Asthmatic	Not reported
Wilson2000b	26	Adults	Asthmatic	Not reported
Wilson2000c	26	Adults	Asthmatic	Not reported
Silkoff2001	15	Adults	Asthmatic	Non smoking
Lim1999	14	Adults	Asthmatic	Non smoking
Kanniess2001	15	Adults	Asthmatic	Non smoking
Pijnenburg2005	37	Children	Asthmatic+Atopic	Non smoking
Haahtela2006	45	Adults	Asthmatic	Mixed
Miraglia2007	12	Children	Asthmatic	Non smoking
Hung2007b	11	Children	Asthmatic	Not reported
Covar2003	30	Children	Asthmatic	Non smoking
FLUNISOLIDE				
Bodini2006	10	Children	Bronquitis	Not reported
BECLOMETHASONE				
Lanz1999	10	Children	Asthmatic	Not reported
Ghiro2003	17	Children	Asthmatic+Atopic	Non smoking
Baraldi1998	13	Children	Rhinitis	Not reported
Silkoff1998	10	Adults	Asthmatic	Non smoking
Ferreira2001	20	Adults	COPD	Ex-smoker
Zietkowski2005a	28	Adults	COPD	Smoking
Zietkowski2005b	19	Adults	COPD	Ex-smoker
Downie2007	18	Adults	Asthmatic+Atopic	Not reported
PREDNISONE				
Gelb2004	10	Adults	Asthmatic	Not reported
Payne2001	23	Children	Asthmatic+Atopic	Non smoking
Szefler2002a	30	Children	Asthmatic+Atopic	Non smoking
Szefler2002b	29	Children	Healthy	Non smoking
Baraldi1999	13	Children	Asthmatic	Not reported
Slats2006	12	Adults	Asthmatic	Not reported
Payne2001(2)	28	Children	Asthmatic	Not reported

Statistic Analysis

From data extraction we realized that we had studies on six anti-inflammatory asthma treatments, and in one case ï Flunisolide ï there was only one study. The most frequent group of patients according to Health Condition is Asthmatic and related to Age Group is Children. Most of the studies do not indicate whether the patients were smokers or not (Table 6).

All studies report a decrease in FENO values following anti-inflammatory treatment (Table 7).

Meta-analysis was performed on each treatment separately

Table 6: Absolute and Relative Frequencies (%) of Study Characteristics

	Frequency	Percentage (%)
Type of Treatment		
Budesonide	19	31
Montelukast	15	24
Fluticasone	12	19
Beclomethasone	8	13
Prednisone	7	11
Flunisolide	1	2
Age Group		
Children	31	50
Adults	30	48
Mixed	1	2
Health Condition		
Healthy	1	2
Asthmatic	46	74
Asthmatic+Atopic	9	15
Bronquitis	2	3
COPD	3	5
Rhinitis	1	2
Smoker		
Smoker	1	2
Non-smoker	22	36
Ex-smoker	2	3
Mixed	4	7
Not Reported	33	53

Table 7: Evolution of FENO (ppb) following Anti-Inflammatory Treatment
All Studies report lower FENO values when treatment is administered (variation always negative)
Var. ï Variation of FENO values due to Treatment; % of Var. ï Percentage of Variation of FENO values due to Treatment

Study	FENO without treatment	FENO with treatment	Var.	% of Var.
MONTELUKAST				
Hung2005	26	16,65	-9	-36
Montuschi2006	45	32	-13	-29
Bonsignore2008	28,2	25,1	-3	-11
Moeller2008	12,9	7,6	-5	-41
Lee2005	33,3	13,5	-20	-59
Montuschi2007	52,2	37,9	-14	-27
Bratton1999	83	58	-25	-30
Hung2007	27,81	16,52	-11	-41
Bisgaard1999	35,3	29,1	-6	-18
Hung2007(2)	25,12	19,65	-5	-22
Zeiger2007b	39,5	30,9	-9	-22
Chuang2007	29,12	18,98	-10	-35
Berkman2003	16,9	13,2	-4	-22
Straub2005	31,4	11,60	-20	-63
Straub2005(2)	29,8	19,00	-11	-36
FLUTICASONE				
Lee2005(2)	6,3	3,30	-3	-48
Fujimoto2006	166,6	70,40	-96	-58
Lee2003b	12,7	7,50	-5	-41
Reddel2008	21,6	12,30	-9	-43
Zietkowski2006	82,4	50,90	-32	-38
Rensen1999	6,3	1,43	-5	-77
Currie2003	9	3,90	-5	-56
Kelly2006	26,9	10,50	-16	-61
Loppow2001	15,6	12,40	-3	-21
Li2006	47,1	39,90	-7	-15
Zeiger2007a	39,5	20,60	-19	-48
Fritscher2009	55	28,10	-27	-49
BUDESONIDE				
Jatakanon1998	36,4	14,80	-22	-59
DalNegro2003a	74,75	26,65	-48	-64
DalNegro2003b	72	33,50	-39	-53
Carrà2001	31,5	17,20	-14	-45

Study	FENO without treatment	FENO with treatment	Var.	% of Var.
BUDESONIDE				
Beck-Ripp2002	13,8	7,70	-6	-44
Lee2003a	12,7	7,50	-5	-41
Kharitonov2002a	17,77	13,40	-4	-25
Kharitonov2002b	20,8	11,40	-9	-45
Wilson2000a	19	9,00	-10	-53
Wilson2000b	19	9,00	-10	-53
Wilson2000c	19	7,00	-12	-63
Silkoff2001	103,5	37,40	-66	-64
Lim1999	42,6	19,70	-23	-54
Kanniess2001	55,2	31,50	-24	-43
Pijnenburg2005	49	11,20	-38	-77
Haahtela2006	59,8	39,40	-20	-34
Miraglia2007	41,1	27,70	-13	-33
Hung2007b	24,56	16,35	-8	-33
Covar2003	48,1	21,50	-27	-55
FLUNISOLIDE				
Bodini2006	38,4	14,90	-24	-61
BECLOMETHASONE				
Lanz1999	48	17,00	-31	-65
Ghiro2003	55,6	36,10	-20	-35
Baraldi1998	271	212,00	-59	-22
Silkoff1998	101	60,60	-40	-40
Ferreira2001	26,2	6,30	-20	-76
Zietkowski2005a	10,61	9,64	-1	-9
Zietkowski2005b	15,66	12,04	-4	-23
Downie2007	14,1	8,00	-6	-43
PREDNISONE				
Gelb2004	30	26,00	-4	-13
Payne2001	11,2	7,50	-4	-33
Szefler2002a	74,9	40,60	-34	-46
Szefler2002b	10,1	5,90	-4	-42
Baraldi1999	14,1	5,90	-8	-58
Slats2006	31,5	17,50	-14	-44
Payne2001(2)	14,9	10,70	-4	-28

FIG B a) Meta-Analysis Results of studies on MONTELUKAST treatment

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Currie2003	3.9	0.8	15	9	2.2	15	10.3%	-5.10 [-6.28, -3.92]
Fritscher2009	28.1	15.3	18	55	35.3	18	5.7%	-26.90 [-44.67, -9.13]
Fujimoto2006	70.4	9.3	34	166.6	22.2	34	8.8%	-96.20 [-104.29, -88.11]
Kelly2006	10.5	10.66	14	26.9	29.56	14	6.1%	-16.40 [-32.86, 0.06]
Lee2003b	7.5	2.6	29	12.7	2.8	29	10.3%	-5.20 [-6.59, -3.81]
Lee2005(2)	3.3	3.18	14	6.3	7.11	14	9.9%	-3.00 [-7.08, 1.08]
Li2006	39.9	27.1	29	47.1	30.3	29	6.6%	-7.20 [-22.00, 7.60]
Loppow2001	12.4	1.1	19	15.6	1.2	19	10.3%	-3.20 [-3.93, -2.47]
Reddel2008	12.3	9.7	23	21.6	13.43	23	9.2%	-9.30 [-16.07, -2.53]
Rensen1999	1.43	0.86	12	6.3	3.34	12	10.2%	-4.87 [-6.82, -2.92]
Zeiger2007a	20.6	2.8	127	39.5	2.65	127	10.3%	-18.90 [-19.57, -18.23]
Zietkowski2006	50.9	35.6	11	82.4	54.8	11	2.1%	-31.50 [-70.12, 7.12]
Total (95% CI)			**345**			**345**	**100.0%**	**-17.19 [-23.55, -10.84]**

Heterogeneity: Tau² = 101.76; Chi² = 1598.85, df = 11 (P < 0.00001); I² = 99%
Test for overall effect: Z = 5.30 (P < 0.00001)

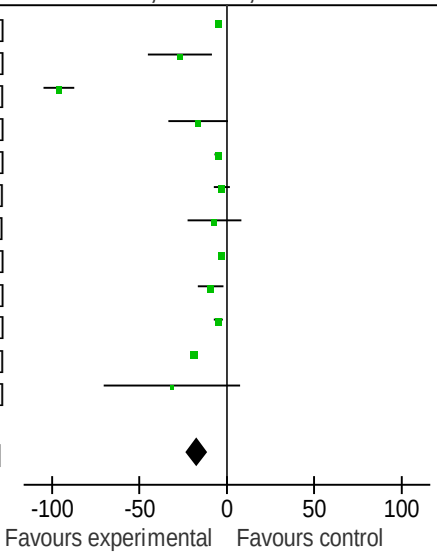


FIG B b) Meta-AnalysisôResults of studies on FLUTICASONE treatment

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Berkman2003	13.2	27.9	19	16.9	52.52	19	1.4%	-3.70 [-30.44, 23.04]
Bisgaard1999	29.1	13.26	26	35.3	11.73	26	8.4%	-6.20 [-13.00, 0.60]
Bonsignore2008	25.1	16.4	25	28.2	21.3	25	5.6%	-3.10 [-13.64, 7.44]
Bratton1999	58	53.69	12	83	69.28	12	0.4%	-25.00 [-74.59, 24.59]
Chuang2007	18.98	7.22	13	29.12	10.12	13	8.4%	-10.14 [-16.90, -3.38]
Hung 2005	16.65	8.18	37	26	12.37	37	10.2%	-9.35 [-14.13, -4.57]
Hung2007	16.51	7.86	11	27.81	13.4	11	6.5%	-11.30 [-20.48, -2.12]
Hung2007(2)	19.65	8.73	20	25.12	8.49	20	9.7%	-5.47 [-10.81, -0.13]
Lee2005	13.5	7.6	20	33.3	15.5	20	7.7%	-19.80 [-27.37, -12.23]
Moeller2008	8.4	5	12	12.9	3.7	12	11.3%	-4.50 [-8.02, -0.98]
Montuschi 2006	32	28.86	17	45	41.23	17	1.7%	-13.00 [-36.92, 10.92]
Montuschi2007	37.9	46.02	14	52.2	14.41	14	1.5%	-14.30 [-39.56, 10.96]
Straub2005	11.6	9.5	30	33.1	12	30	9.5%	-21.50 [-26.98, -16.02]
Straub2005(2)	19	8.5	24	29.8	10	24	9.8%	-10.80 [-16.05, -5.55]
Zeiger2007b	30.9	29.86	127	39.5	29.3	127	8.0%	-8.60 [-15.88, -1.32]
Total (95% CI)			**407**			**407**	**100.0%**	**-10.18 [-13.50, -6.86]**

Heterogeneity: Tau² = 22.24; Chi² = 39.08, df = 14 (P = 0.0004); I² = 64%
Test for overall effect: Z = 6.01 (P < 0.00001)

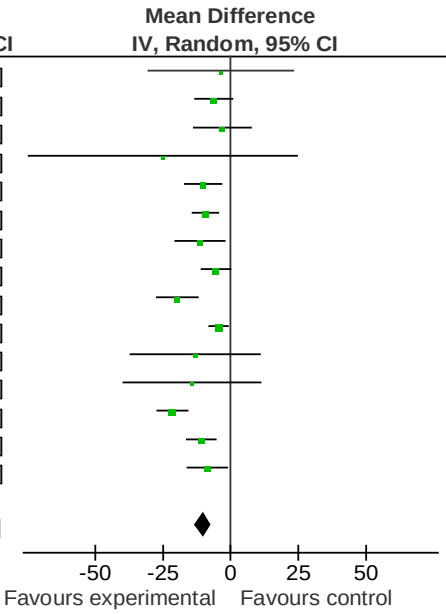


FIG B c) Meta-AnalysisôResults of studies on BUDESONIDE treatment

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Beck-Ripp2002	7.7	1.2	54	14.8	1.9	54	7.2%	-7.10 [-7.70, -6.50]
Carrà2001	17.2	6.48	11	31.5	12.44	11	6.0%	-14.30 [-22.59, -6.01]
Covar2003	21.5	172.81	30	48.1	115.84	30	0.4%	-26.60 [-101.05, 47.85]
DalNegro2003a	26.65	11.37	10	74.75	47.96	10	2.0%	-48.10 [-78.65, -17.55]
DalNegro2003b	33.5	13.65	10	72	33.63	10	3.0%	-38.50 [-61.00, -16.00]
Haahtela2006	39.4	25	45	59.8	40	45	4.7%	-20.40 [-34.18, -6.62]
Hung2007b	16.35	7.61	11	24.56	14.42	11	5.7%	-8.21 [-17.85, 1.43]
Jatakanon1998	14.8	3.58	5	36.4	4.02	5	6.7%	-21.60 [-26.32, -16.88]
Kanniess2001	31.5	1.2	15	55.2	1.2	15	7.2%	-23.70 [-24.56, -22.84]
Kharitonov2002a	13.4	7.65	26	17.77	6.2	26	6.9%	-4.37 [-8.15, -0.59]
Kharitonov2002b	11.4	7.9	26	20.8	14.02	26	6.5%	-9.40 [-15.59, -3.21]
Lee2003a	7.5	2.6	29	12.7	2.8	29	7.1%	-5.20 [-6.59, -3.81]
Lim1999	19.7	3.2	14	42.6	7.8	14	6.8%	-22.90 [-27.32, -18.48]
Miraglia2007	27.7	4.7	12	41.1	4.5	12	6.9%	-13.40 [-17.08, -9.72]
Pijnenburg2005	11.2	12.47	37	49	142.49	37	1.0%	-37.80 [-83.89, 8.29]
Silkoff2001	37.4	20.91	15	103.5	64.29	15	1.7%	-66.10 [-100.31, -31.89]
Wilson2000a	9	5	26	19	11	26	6.8%	-10.00 [-14.64, -5.36]
Wilson2000b	9	5	26	19	11	26	6.8%	-10.00 [-14.64, -5.36]
Wilson2000c	7	3	26	19	11	26	6.8%	-12.00 [-16.38, -7.62]
Total (95% CI)			**428**			**428**	**100.0%**	**-15.56 [-20.61, -10.52]**

Heterogeneity: Tau² = 92.45; Chi² = 1142.62, df = 18 (P < 0.00001); I² = 98%
Test for overall effect: Z = 6.05 (P < 0.00001)

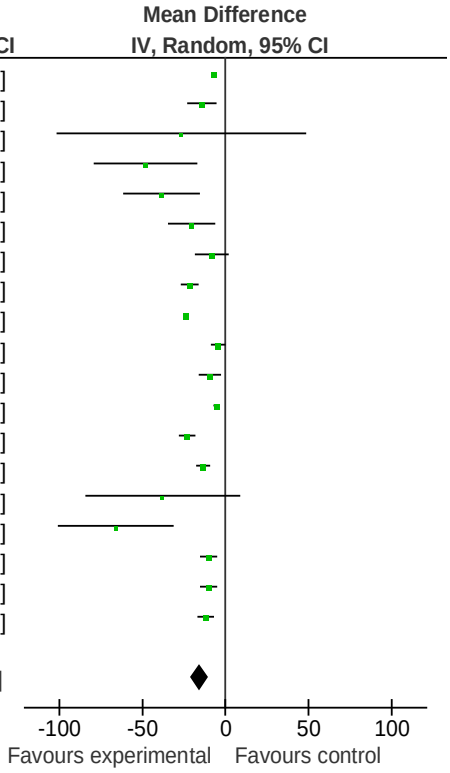


FIG B d) Meta-AnalysisôResults of studies on FLUNISOLIDE treatment; only one study was included

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Bodini2006	14.9	3.38	10	38.4	4.53	10	100.0%	-23.50 [-27.00, -20.00]
Total (95% CI)			**10**			**10**	**100.0%**	**-23.50 [-27.00, -20.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 13.15 (P < 0.00001)

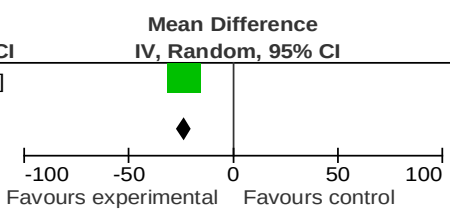


FIG B e) Meta-AnalyisisôResults of studies on BECLOMETHASONE treatment

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Baraldi1998	212	20	13	271	18	13	12.1%	-59.00 [-73.63, -44.37]
Downie2007	8	6.5	18	14.1	6.5	18	15.6%	-6.10 [-10.35, -1.85]
Ferreira2001	19.9	50.6	20	26.2	63.95	20	5.5%	-6.30 [-42.04, 29.44]
Ghiro2003	36.1	4.6	17	55.6	8.7	17	15.5%	-19.50 [-24.18, -14.82]
Lanz1999	17	1	10	48	8	10	15.4%	-31.00 [-36.00, -26.00]
Silkoff1998	60.6	31.1	10	101	60.4	10	4.4%	-40.40 [-82.51, 1.71]
Zietkowski2005a	9.64	2.74	28	10.61	4.6	28	15.9%	-0.97 [-2.95, 1.01]
Zietkowski2005b	12.04	3.2	19	15.66	8.59	19	15.6%	-3.62 [-7.74, 0.50]
Total (95% CI)			**135**			**135**	**100.0%**	**-18.73 [-29.06, -8.41]**

Heterogeneity: Tau² = 173.43; Chi² = 205.28, df = 7 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.56 (P = 0.0004)

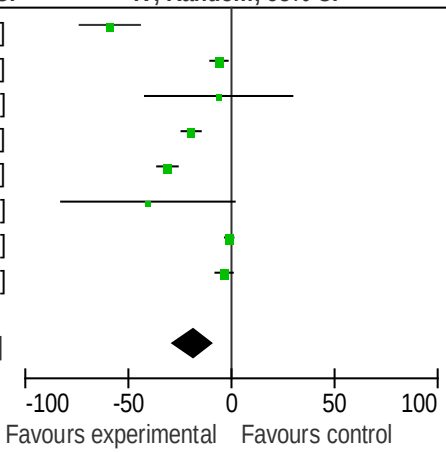
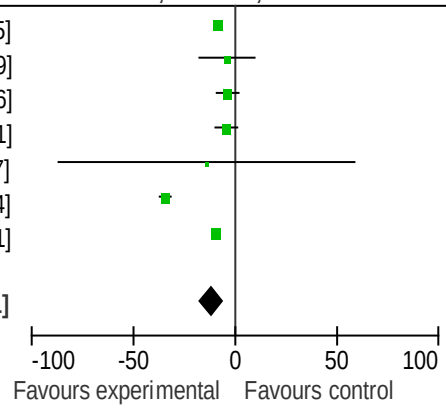


FIG B f) Meta-AnalysisôResults of studies on PREDNISONE treatment

Study or Subgroup	With Mean	With SD	With Total	Without Mean	Without SD	Without Total	Weight	Mean Difference IV, Random, 95% CI
Baraldi1999	5.9	0.7	13	14.1	1.8	13	19.0%	-8.20 [-9.25, -7.15]
Gelb2004	26	16	10	30	15	10	9.6%	-4.00 [-17.59, 9.59]
Payne2001	7.5	6.23	23	11.2	11.27	23	16.7%	-3.70 [-8.96, 1.56]
Payne2001(2)	10.7	9.7	28	14.9	10.57	28	16.6%	-4.20 [-9.51, 1.11]
Slats2006	17.5	79.67	12	31.5	100.98	12	0.7%	-14.00 [-86.77, 58.77]
Szefler2002a	40.6	4.6	30	74.9	6.2	30	18.4%	-34.30 [-37.06, -31.54]
Szefler2002b	11.1	0.8	29	20.2	1.4	29	19.1%	-9.10 [-9.69, -8.51]
Total (95% CI)			**145**			**145**	**100.0%**	**-11.39 [-17.37, -5.41]**

Heterogeneity: Tau² = 48.70; Chi² = 326.17, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.73 (P = 0.0002)



DISCUSSION

To determine the effects of anti-inflammatory asthma medication on FENO values we conducted a Systematic Review and a Meta-analysis on the current literature. 53 studies were included on our review. From these, 62 interventions were analyzed separately and FENO values were extracted.

We noticed that all the interventions showed a decrease FENO values due to the addition of the anti-inflammatory treatment. Some of the results were unexpected. According to the literature Oral Corticosteroids (such e.g. Prednisone) ought to produce the largest reduction on FENO values, followed by Inhaled Corticosteroids (e.g. fluticasone, budesonide, flunisolide, beclometasone). In our study we found that the drug that causes the largest decrease was Flunisolide (-23,50ppb [-27,0 to -20,0]). Montelukast (Oral Corticosteroid), which was thought to be ineffective [66,67] has the smallest effect (-10,18ppb [-13,5 to -6,86]).

We conclude that FENO values decrease when anti-inflammatory drugs are administered, even when variables such as sex or age are taken into account. This is easily explained by the fact that FENO is

a biomarker of the airways inflammation [2-7]. So, if inflammation decreases with anti-inflammatory treatment, FENO values also decrease. We also conclude that Montelukast decreases FENO as well.

Limitations

The results we obtain by doing a meta-analysis show that the studies have high heterogeneity values, which decreases the reliability of our conclusions. We were also unable to find studies on all the anti-inflammatory treatments, which makes it impossible to extend our results to all existing anti-inflammatory treatments.

We performed our search on just three data bases, which we consider to be the most important databases on Clinical Care. We found 53 studies and only 18 studies weren't available. This means that we studied a representative sample of currently existing studies on the subject.

Recommendations

Future studies are needed to determine the causes of heterogeneity among groups with different age, sex, health condition (where patients with asthma have different intensity levels) and treatment dosage. FENO values related to asthma are still inadequately studied.

As notes above, anti-inflammatory asthma treatment decreases FENO values, which supports the relation between NO production and the airways inflammation. Here again, non-evasive FENO measurements [3] could be of major importance for asthma management, specifically on terms of in preventing exacerbation, which follows an increase of the airways inflammation.

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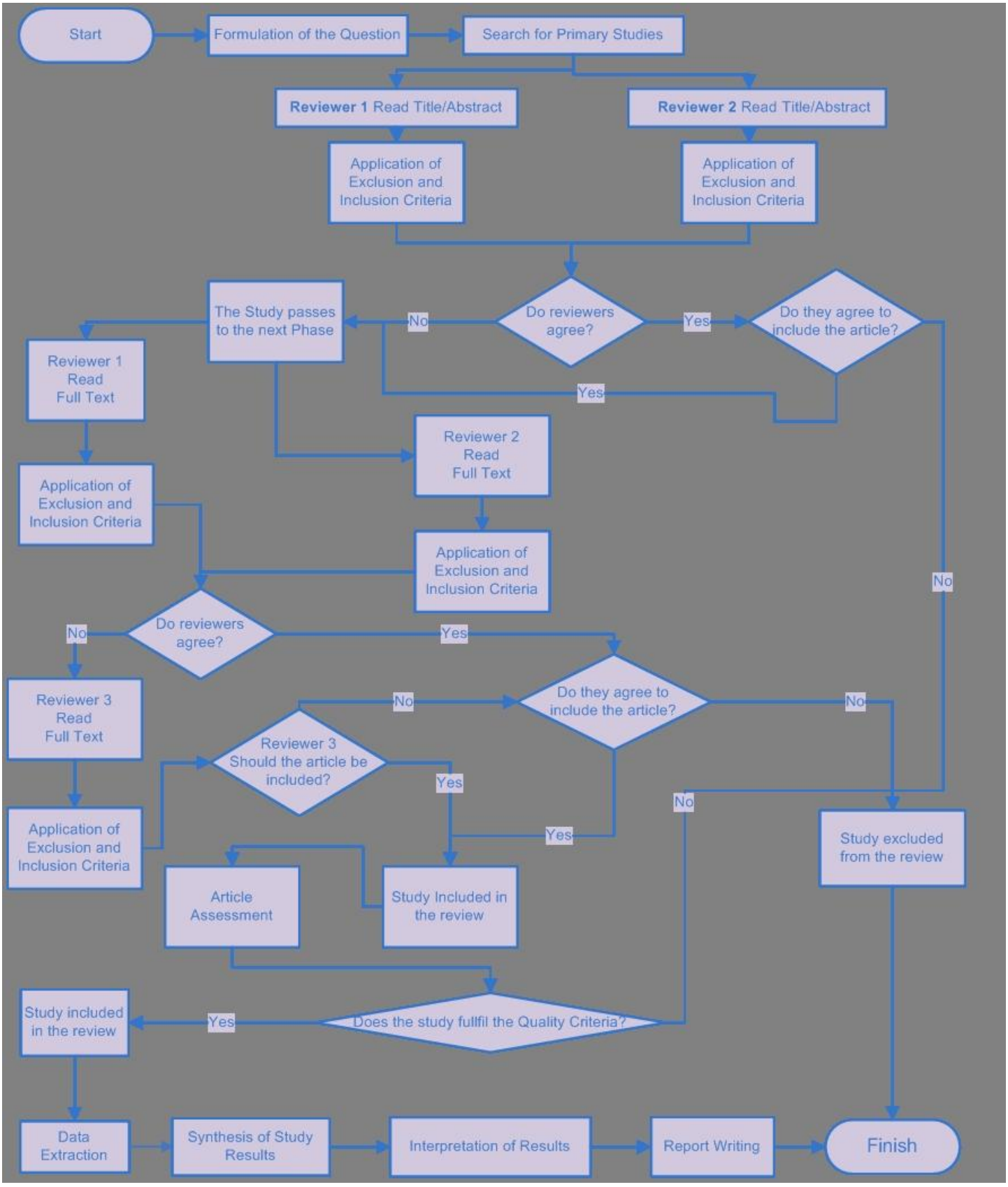
APPENDIX 1 ï Systematic Review Methods Flowchart



APPENDIX 2 ï Data Bases Queries

PUBMED:

(Exhaled Nitric Oxide OR FENO OR ENO) AND (Leukotriene Antagonists OR Glucocorticoids OR Montelukast OR Zafirlukast OR Zileuton OR Fluticasone OR Budesonide OR Triamcinolone OR Flunisolide OR Beclomethasone OR Mometasone OR Prednisone OR Methylprednisolone OR Hydrocortisone)

LIMITS: articles published since 1990; data collected on HUMANS; Clinical Queries: Therapy and Sensitive Search ï PUBMED.

SCOPUS:

(Exhaled Nitric Oxide OR FENO OR ENO) AND (Leukotriene Antagonists OR Glucocorticoids OR Montelukast OR Zafirlukast OR Zileuton OR Fluticasone OR Budesonide OR Triamcinolone OR Flunisolide OR Beclomethasone OR Mometasone OR Prednisone OR Methylprednisolone OR Hydrocortisone) AND (humans OR patients OR volunteers) AND (clinical trial OR therapy OR ñtherapeutic useò)

LIMITS: articles published since 1990

ISI Web of Knowledge:

(Exhaled Nitric Oxide OR FENO OR ENO) AND (Leukotriene Antagonists OR Glucocorticoids OR Montelukast OR Zafirlukast OR Zileuton OR Fluticasone OR Budesonide OR Triamcinolone OR Flunisolide OR Beclomethasone OR Mometasone OR Prednisone OR Methylprednisolone OR Hydrocortisone) AND (humans OR patients OR volunteers) AND (clinical trial OR therapy OR ñtherapeutic useò)

APPENDIX 3 – Data Extraction Form

STUDY'S IDENTIFICATION

Article's Title

Last Name of the First Author

Publication Date

Data Base

PATIENTS

Number of Patients

Number of Male Patients

Number of Female Patients

Health Condition (Healthy, Asthmatic, Asthmatic+Atopic, Bronchitis, Chronic Obstructive Pulmonary Disease, Rhinitis)

Smoker (Smoker, Ex-smoker, Non-smoker, Mixed, Unknown)

Age Group (Children, Adults, Elderly, Mixed)

TREATMENT

Type of Treatment (all drugs presented on Table 1)

Dosage

FENO EVOLUTION

FENO without treatment (ppb)

FENO with treatment (ppb)

FENO evolution (decrease, increase, maintain)