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REVIEW ARTICLE

Use of asthma control indicators in measuring inhaled corticosteroid effectiveness in asthmatic smokers: a systematic review

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Abstract

Objective: The objective of this review is to explore how current research measures the effectiveness of inhaled corticosteroids (ICS) in smokers with asthma. **Data sources:** PubMed, CINAHL and PsycINFO databases were searched for combinations of terms relating to asthma, tobacco use and ICS effectiveness. **Study selections:** The search was limited to articles published between 2004 and 2015, in English language. Studies met inclusion criteria if reporting the use of guideline-based asthma control indicators to measure the therapeutic effects of ICS or ICS combination therapies. This review did not exclude articles based on study design. Data were extracted and summarized to describe how indicators were measured across studies in order to characterize and describe the effects of ICS in smokers. **Results:** Thirteen studies were included in this review. Six of these 13 studies used only one indicator to measure asthma control in smokers and ICS was found to improve asthma in only one of six of these studies. Of studies evaluating combination therapy, three of four studies reported a therapeutic benefit to smokers. In these studies of combination therapy multiple indicators of control were measured to assess drug effects. **Conclusions:** To assess the therapeutic benefit of ICS drugs in smokers, multiple indicators should be measured to determine if current therapy is improving asthma control. Asthma therapy should then be adjusted based on the patient's current asthma status. The development of clinical treatment guidelines for asthmatic smokers may help clinicians make best-practice, evidence-based recommendations in order to optimize care for these patients.

Keywords

Asthma guidelines, evidence-based care, inhaled corticosteroids, long-term therapy, medication effectiveness, pharmacotherapy, tobacco use

History

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Introduction

In the USA, 25–35% of asthmatics smoke [1,2]. Albeit, specific asthma treatment recommendations for this patient population are scarce. The National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Review-3 asthma guidelines addressed the potentially diminished responsiveness of inhaled corticosteroids (ICS) in smokers; however, alternate treatment recommendations for smokers are not described [3]. ICS work by reducing inflammation in the airways of the lungs, thus reducing hypersensitivity to allergens and to environmental or household triggers [3]. A number of studies have evaluated ICS responsiveness in smokers [4–8]; however, a consensus on the use and clinical effectiveness of these drugs in smokers has not been determined. Asthma drug trials often exclude smokers [9], therefore available treatment options may not be best for these patients. Oftentimes, to optimize treatment for smokers, many physicians elect to prescribe higher doses of ICS or combination therapies waging the potentially higher risks associated with these drugs [3,9].

According to the NHLBI, asthma control is classified as well controlled, not well controlled or very poorly controlled

[3]. Six indicators are used to make this classification: frequency of daytime symptoms, frequency of night-time awakenings due to asthma, use of quick-reliever medication, interference with normal activity due to asthma, lung function and frequency of exacerbations requiring oral steroids for treatment [3]. Validated patient self-assessments such as the Asthma Control Test (ACT), Asthma Therapy Assessment Questionnaire (ATAQ) and the Asthma Control Questionnaire (ACQ) may also be used as measures of control [3]. These tools capture information relating to the aforementioned indicators. Definitions of each indicator and validated patient-self assessment can be found in Table 1. Based on NHLBI asthma guidelines it is recommended that multiple indicators be used to make conclusions on the patients' level of control [3]. Specifically, NHLBI states that these indicators be evaluated based on the patient's 2–4 week recall of asthma symptoms in addition to lung function testing [3]. Asthma therapy should then be prescribed based on this comprehensive assessment [3].

ICS therapies include a range of medications from low-dose ICS to treatment with a high dose ICS and long-acting beta-2 agonist (LABA) combination drug [3].

It is recommended that asthmatics receive asthma control assessments every 1–6 months or every 2–6 weeks if asthma is not currently controlled to ensure that prescribed

Table 1. Definition of variables.

Variable	Definition
Asthma control indicators	
Symptom days	Number of days per week the patient experiences asthma symptoms (coughing, wheezing, shortness of breath, tightness in chest).
Night-time awakenings	Number of nights per week the patient awakes due to asthma symptoms.
SABA use	Number of days a SABA used for symptom control. SABA, a quick reliever medication used only when a patient is experiencing asthma symptoms. Also known as a rescue inhaler.
Interference w/normal activity	Degree to which patient is limited to participate in normal daily activities due to asthma.
Lung function (FEV1)	FEV1-The amount of air that can be expelled from the lungs after one second of forceful exhalation. Used as a principal measure in determining lung function impairment in asthmatics.
Exacerbations requiring oral steroids	Number of asthma exacerbations requiring a burst of oral steroids in the last year.
Other variables	
Asthma control assessments	Validated assessment tools used to assess asthma control ACT – Asthma Control Test ATAQ – Asthma Therapy Assessment Questionnaire ACQ – Asthma Control Questionnaire – evaluates domains *For ATAQ and ACQ a lower score indicates better control. Higher scores using the ACT indicates better control of asthma.
Pack years	A measurement of the number of cigarettes a person has smoked over their lifetime. 1 pack-year is equivalent to 1 pack or 20 cigarettes per day for one year. Calculated by multiplying the number of packs smoked daily by the number of years the patient has smoked.

^aAdapted from NHLBI [3].

therapy is meeting treatment goals [3]. Without a complete assessment based on multiple indicators, the patients level of control may be under- or overestimated and therefore under- or over-treated. For smokers with asthma, level of control is assessed in the same manner although smokers do experience increased asthma morbidity compared to non-smokers [10]. NHLBI recommends that smokers receive cessation counseling, as previously mentioned; however, specific pharmacotherapy recommendations for smokers are not described [3].

In this review, researchers evaluated how asthma control indicators were used across studies to assess the effects of ICS therapy in asthmatic smokers [3]. Although single measures such as lung function are relevant in determining asthma status, according to national guidelines, control of asthma should be assessed by measuring of multiple indicators in order to provide a full assessment of the patient’s disease state [3]. Many studies addressing asthma treatment have employed these indicators to assess ICS responsiveness [4–8]; however, few studies specific to asthmatic smokers have used them [11].

Methods

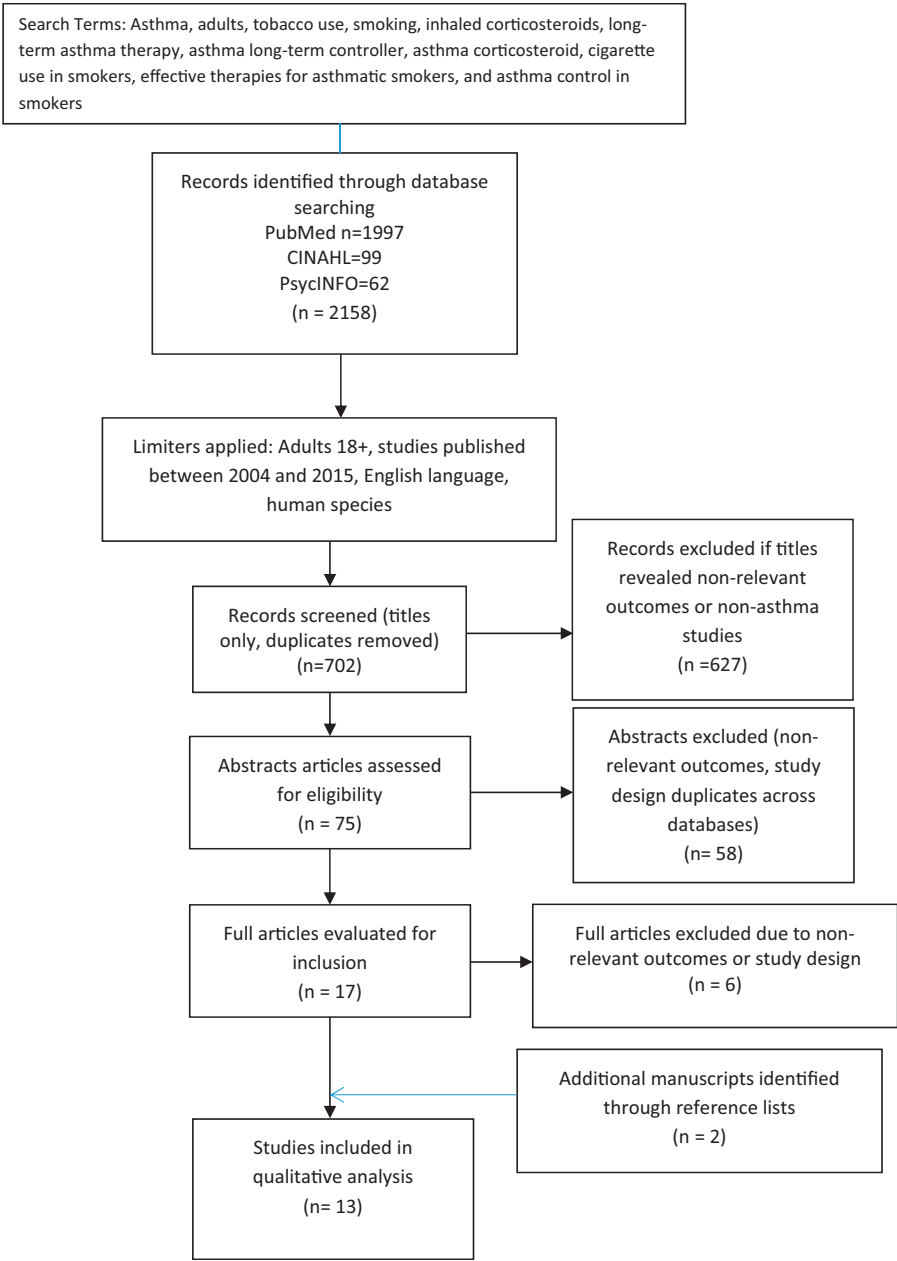
A systematic search of the PubMed, CINAHL and PsycINFO databases was conducted between 20 August 2014 and 5 September 2014 based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) [12]. The initial search included combinations of terms relating to asthma, ICS (i.e. long-term asthma medication, long-term asthma therapy, asthma controller medications, asthma controller therapy) and tobacco use (i.e. smoking, cigarette use, cigarette smoking). A data extraction form was created in order to collect relevant study information from each article including lead author name, year of publication, study design, duration, mean age of participants, sample size including the sample size of smokers, pack years of enrolled smokers, type and dosage of ICS therapy, asthma guideline indicators used as measures,

as well as major results. Two researchers performed the initial search and conducted the appraisal of articles based on the aforementioned domains.

The search was limited to articles published between 2004 and 2015 and to studies of adult subjects published in English language. Inclusion criteria included the use of at least one asthma control indicator (i.e. frequency of daytime symptoms, frequency of night-time awakenings due to asthma, use of quick-reliever medication, interference with normal activity due to asthma, lung function, frequency of exacerbations requiring oral steroids for treatment, or validated questionnaire score) to assess ICS or ICS/LABA effectiveness. Due to the limited availability of published research on this topic, authors did not exclude articles based on study design or setting. All studies of adult smokers prescribed ICS-only or ICS/LABA therapy for the treatment of asthma were therefore included in this review such as articles comparing ICS response in smokers and nonsmokers as well as pre-post studies of smokers on ICS. Relevant outcomes under study included the therapeutic effects of ICS as determined by the assessment of at least one asthma control indicator in selected articles. Studies were excluded if ICS response was measured using sputum eosinophil counts or nitric oxide values. Although such measures may be helpful in evaluating airway inflammation in patients with asthma, they are not guideline-based indicators of asthma control [3].

Article titles were reviewed to identify and exclude reports with nonrelevant outcomes and to remove duplicates within each database. A review of abstracts was then conducted to assess whether the remaining articles met inclusion criteria. Duplicates across the three databases were removed at this time. The remaining articles were reviewed in full and included in this review if criteria were met. Additional articles were identified from the reference lists of selected articles. Researchers extracted data across studies and recorded findings in data extraction forms, as described previously. Researchers summarized and synthesized these findings to

Figure 1. Article search and screening process for the effectiveness of ICS therapy in asthmatic smokers.



evaluate inferences and conclusions made on the effects of ICS as based on indicators measured across studies. This included the synthesis of data to determine the prevalence of asthma control indicators across studies, the number of studies using various types and dosages of ICS therapies, the prevalence of studies reporting ICS combination therapy, and the effects of pack years on ICS response.

Results

Study selection

Figure 1 presents a diagrammatic flow of the process and search terms used to conduct the review. The search of the PubMed ($n = 1997$), CINAHL ($n = 99$) and PsycINFO ($n = 62$) databases resulted in identification of 2158 articles. After applying limiters, 702 articles remained. Titles of these articles were reviewed for relevance to outcomes of interest, and 627 articles were excluded, including all duplicates

within individual databases. The abstracts for the remaining articles ($n = 75$) were reviewed. Fifty-eight articles were then excluded due to nonrelevant outcomes, as were duplicates across the three databases. Full articles from the remaining 17 were then reviewed for inclusion. During this process, six articles were excluded due to nonrelevant outcomes, such as incomplete reporting of asthma control indicators or the failure to report outcomes of smokers or ICS users. Two articles identified in the reference lists of selected articles were added to the review. Summaries of the 13 selected studies are presented in Table 2.

Characteristics of studies

The mean age of participants ranged between 25 and 58 years across studies [10,13–24]. Of the included studies, 11 of 13 were prospective [10,13–17,19,21–24], including 6 randomized controlled trials (RCTs) [10,14–16,19,24]. Types of

Table 2. Results of 13 studies of the effectiveness of ICS therapy for asthmatic smokers.

Reference	Year	Study design	Mean age of participants in years	N (smokers)	Study duration	Mean pack years of smokers	ICS daily treatment (dose)	Asthma guideline endpoints	Results
Brusselle et al. [13]	2012	Observational prospective, open label, non-interventional, multicenter	48.6 ± 16.9	619 (123)	8–14 months	NA	Beclomethasone dipropionate 100 µg/formoterol 6 µg	ACQ, FEV1/PEF	ICS treatment associated with significant increases in FEV1 and ACQ scores in smokers and nonsmokers ($p < 0.0001$).
Schayck et al. [14]	2012	Randomized, controlled parallel, multicenter	38.8 ± 12.4	8424 (886)	6 months	5.9 ± 4.9	Budesonide 160 µg/formoterol 4.5 µg 1 puff twice per day or 2 puffs twice per day	Day symptoms, night awakenings, SABA use, ACQ, FEV1/PEF	FEV1 values similar between smokers and nonsmokers at baseline ($p = 0.1817$). PEF differed ($p = 0.0026$). Significant improvements in day symptoms, night awakenings, SABA use, ACQ in smokers receiving two puffs compared to 1 puff.
O'Byrne et al. [15]	2009	Randomized, placebo-controlled, double blind	34 ± 10.8	2924 (492)	36 months	NA	Budesonide (400 µg) 1 puff per day	FEV1, symptom-free days	Lung function improvements noted in smokers from baseline ($p < 0.001$).
Lazarus et al. [16]	2007	Randomized, placebo-controlled, double-blind, multicenter	29.06 ± 6.54	83 (39)	8 weeks	7.0 ± 4.0	Beclomethasone (160 µg)	FEV1/PEF symptoms	8 week change in FEV1 from baseline nonsignificant in smokers using ICS ($p = NS$).
Lange et al. [17]	2006	Longitudinal, noninterventional	Group 1: 57.2 ± 11.3, women; 51.7 ± 12.7, men Group 2: 57.9 ± 9.8, women; 58.4 ± 8.7, men	234 (75)	10 years	NA	ICS unspecified	FEV1	Smokers on ICS had improvements in lung function compared to smokers not on ICS therapy ($p = 0.035$).
Dijkstra et al. [18]	2006	Longitudinal, noninterventional	28 (21–37) ^a	122 (55)	36 years	0.1 (0–5.6) ^a	ICS unspecified	FEV1	No significant improvement in smokers with ≥5 pack years. Significant increases in FEV1 after ICS administration in men ($p = 0.0097$) compared to women ($p = 0.94$).
Tomlinson et al. [19]	2005	Randomized, double-blind, parallel group	46.0 ± 3.0 ^b 43.0 ± 14.0 ^c	95 (40)	12 weeks	25.0 ± 15.0	Beclomethasone (400 µg) and beclomethasone (2000 µg)	ACQ, FEV1/PEF, symptoms, SABA use	Lung function improvements noted in nonsmokers receiving 400 µg but not smokers ($p = 0.019$). Morning PEF values improved in smokers using 2000 µg. No difference in FEV1 or PEF in smokers using 400 µg and 2000 µg. No differences in symptoms across treatment groups. Improvements in ACQ occurred in nonsmokers compared to smokers across both treatments ($p = 0.0130$).
Harmsen et al. [20]	2010	Retrospective	30.9 ± 8.0 ^b 27.7 ± 8.2 ^c	793 (357)	NA	5.0 (2.0–13.0) ^a	ICS unspecified	FEV1	Nonsmokers have significantly higher FEV1 values than smokers using ICS ($p = 0.002$).
Tsoumakidou et al. [21]	2007	Prospective	31.0 ± 6.0 ^b 32.0 ± 6.0 ^c	55 (24)	NA	10.0 (5.0–36.0) ^a	ICS unspecified	FEV1/PEF	No difference in lung function between smokers using ICS and nonsmokers.

(continued)

Reference	Year	Study design	Mean age of participants in years	N (smokers)	Study duration	Mean pack years of smokers	ICS daily treatment (dose)	Asthma guideline endpoints	Results
Chaudri et al. [22]	2006	Prospective controlled	45.7 ± 6.8 ^b 49.5 ± 9.3 ^c	10 (10)	12 months	36.5 ± 11.7 ^b 36.1 ± 21.2 ^c	ICS undisclosed	Day symptoms, night symptoms, SABA use, FEV1/PEF, asthma control score	Improvements in FEV1 in cessation group compared to those who continued to smoke ($p = 0.031$). Asthma control scores improved in cessation group ($p = 0.021$).
Clearie et al. [10]	2012	Randomized, placebo-controlled, double-blind	37.8 ± 2.8 ^b 38.9 ± 3.9 ^c	31 (15)	11 weeks	13.9 ± 2.6	Fluticasone (250 µg) Fluticasone/salmeterol (125 µg/25 µg)	ACQ FEV1	Significant improvement in ACQ score in nonsmokers using both fluticasone ($p = 0.01$) and fluticasone with salmeterol ($p = 0.02$). No significant score improvements in smokers using fluticasone ($p = 0.31$) or fluticasone with salmeterol ($p = 0.32$). Improvements in lung function (FEV1) in nonsmokers compared to smokers using fluticasone ($p = 0.02$). Smokers and nonsmokers benefitted similarly to fluticasone with salmeterol ($p = 0.84$).
Muller et al. [23]	2011	Noninterventional, cross-sectional	48 (19–84) ^{a,f} 47 (18–86) ^{a,g}	111 (39)	NA	19.0 ± 3.6	Budesonide/formoterol and Beclomethasone/formoterol Fluticasone/salmeterol	Day symptoms, nighttime awakenings, limitation in physical activity, SABA use, exacerbations requiring ED/hospitalization FEV1	Of smokers, 51.3% attained asthma control using medications under study. 25.6% were classified as partially controlled, 23.1% classified as uncontrolled.
Telenga et al. [24]	2013	Double-blind, double-dummy and open label (at 50 weeks)	25 (25–35) ^{a,d} 38 (28–41) ^{a,e} 25 (25–35) ^{a,b}	114 (30)	1 year	7.4 (2.5–14.1) ^a	Fluticasone 500 µg Fluticasone 2000 µg	FEV1	Significant improvement in FEV1 in former and never smokers, $p = 0.011$ and $p < 0.001$, respectively. Marginal improvements in FEV1 noted in smokers ($p = 0.058$).

^aInterquartile range value reported.^bValue for smokers.^cValue for nonsmokers.^dValue for never-smokers.^eValue for former smoker.^fMetered dose inhaler users.^gDry powder inhaler users.

ICS therapy varied. In most studies, the form of ICS therapy was unspecified [17,18,20–22]. Of ICS-only studies, budesonide was the chosen ICS in only one study [15], beclomethasone in two studies [16,19] and fluticasone in one [24]. Combination therapies using budesonide, beclomethasone or fluticasone in addition to a LABA were used in four studies [10,13,14,23].

Various asthma control indicators were measured across included articles, the most common being lung function, which was assessed in all 13 studies [10,13–24]. In these studies lung function was reported as forced expiratory volume in 1 s (FEV1) and/or peak expiratory flow (PEF) values (Table 1). These measures provide diagnostic assessments of asthma status [3]. Other commonly used indicators included symptom days which was measured in six studies [14–16,19,22,23], followed by the use of validated questionnaires in five studies [10,13,14,19,22]. See Table 2 for a complete list of indicators measured across included studies.

Use of asthma control indicators

Regarding the number of indicators measured, 6 of 13 studies used only one indicator to determine ICS effectiveness [10,17,18,20,21,24]. Across these six studies the sole indicator used was lung function [10,17,18,20,21,24]. In five of six studies measuring only lung function, it was concluded that ICS therapy was ineffective or nonoptimal for smokers [10,18,20,21,24]. This also includes one study where improvements were reported as marginal [24]. In contrast, for studies measuring two indicators, two of three concluded that ICS significantly improved asthma control for smokers [13,15,16]. In one study, four indicators [(ACQ, lung function, symptom days, short acting beta agonist (SABA) use] were used to assess ICS effects [19]. Lung function improvements were observed in nonsmokers receiving low and high dose ICS; however, nonsignificant improvements were noted in smokers who received both forms of treatment [19]. Three studies used five indicators to assess effectiveness of ICS in smokers [14,22,23]. However, in two of these studies, the effects of ICS combination therapy were assessed rather than ICS-only therapy [14,23]. In both of these studies combination therapy led to significant improvements in asthma control in smokers [14,23].

Treatment type

ICS-only therapy includes the use of ICS without the addition of a LABA. Of studies included in this review, 8 of 13 assessed the therapeutic effectiveness of ICS-only therapy in improving symptoms. In these studies, three of eight found ICS to be effective in improving asthma in smokers [10,15,18]. Of studies reporting specific forms of drugs used, budesonide [14,16,23] and beclomethasone [13,16,19,23] were the most common forms of ICS, which included these drugs in their combination forms. ICS improved asthma control in two of three of studies involving budesonide and in two of four studies reporting use of beclomethasone [13–16,19,22,23]. Fluticasone was used in three studies [10,23,24]. In two of these studies, the use of fluticasone did not improve asthma control in smokers

[10,24]. Five studies did not specify the type of ICS used [17,18,20–22].

Smoking history

Pack-years were reported as range or as mean values. One study reported a range of less than 5 pack years for smokers [18], while five studies reported means between 5 and 10 pack years for smokers [14,16,20,21,24]. Five studies [10,18,19,22,23] of smokers with more than 10 mean packs years were also included in the review which included two studies [19,22] with means values over 20 pack years. ICS effectiveness across studies did vary by pack year. Across studies of less than 10 mean pack years, one of six studies reported significant improvements in smokers using some form of ICS therapy [14]. In this study, combination medication proved effective in treating smokers with an average of 5.9 (4.9) pack years [14]. Similarly, in studies of more than 10 mean pack years [10,19,22,23], only one study [23], also of combination medication, reported therapy to be effective in smokers. In three studies, mean or range pack years were not reported, however, in these studies ICS were found to be effective in improving asthma control in smokers [13,15,17].

Discussion

Summary of evidence

Use of asthma control indicators

The NHLBI asthma clinical guidelines identify indicators that when evaluated provide an assessment of patient's level of asthma control. Guidelines recommend that multiple indicators be measured concurrently in order to attain a comprehensive assessment of the patient's asthma status [3]. It is with this assessment that clinicians can determine patient risk for future symptoms or exacerbations. As ICS therapy is the most common form of long-term asthma therapy, it is necessary to properly evaluate its effectiveness in all subpopulations of patients, including smokers. Across studies included in this review, ICS effectiveness was measured by various indicators of control; however, as previously stated, many studies used only one indicator (i.e. lung function) to make this assessment. Although lung function, as measured by FEV1 or PEF, provides a diagnostic assessment, it should be used in combination with other measures to ensure that asthma status is assessed in full [3]. Several studies included in our review use only lung function to determine ICS responsiveness and conclude, based on this single indicator, that ICS are ineffective [10,17,18,20,21,24]. Lung function is an important indicator as airway obstruction may be present prior to the development of asthma symptoms in some patients [25]. Nonetheless, the monitoring of other indicators such as symptoms and nighttime awakenings must not be discounted. Small airway obstruction may not be detected with some forms of lung function testing; however, symptoms or asthma warning signs may be present [26]. Additionally, regarding patient self-management of asthma, symptoms may present before pulmonary function testing can be performed. Prior to making conclusions based on single indicators of asthma control, researchers should aim to conduct thorough asthma

control assessments of their patients as identifying the appropriate level of control will dictate the type and amount of asthma therapy needed. The use of multiple indicators allows clinicians to choose the most conservative course of therapy based on a guideline-based patient assessment.

Treatment type

Of ICS-only studies included in this review, three of eight found ICS to be effective [10,15,18]. In two of these studies [10,15] only two indicators were used to assess improvement in asthma, and in one study [18] only one indicator was used. Alternately, in studies of combination or ICS-LABA drugs [10,13,14,23], three of four studies found therapy to be effective in smokers [10,13,14]. In one study by Clearie et al. researchers compared the benefits of ICS-only therapy and combination drug therapy in asthmatic smokers. Study participants received either ICS-only, in the form of fluticasone 250 µg, or combination therapy, in the form of fluticasone/salmeterol (125 µg/25 µg) for two weeks [10]. Changes in ACQ score and lung function were assessed to determine drug effectiveness. Significant ACQ score improvements were noted in nonsmokers receiving both ICS-only and combination therapy ($p=0.01$ and $p=0.02$, respectively), however, not in nonsmokers ($p=0.31$ and $p=0.32$, respectively) [10]. Combination therapy was found to improve lung function as measured by FEV1 in smokers ($p=0.003$); however, in smokers using ICS-only therapy significant improvements were not observed ($p=0.76$) [10]. Although an increased risk of adverse events (i.e. asthma-related death and severe asthma exacerbations) is related to combination medications [3], based on the indicators measured, the addition of a LABA may optimize asthma control in smokers. Clinical practice guidelines recommend 2–6 weeks of consistent ICS use prior to assessing therapeutic response to prescribed therapy [3]. Therefore, when evaluating patients at risk for increased asthma morbidity, a longer intervention period may be needed as two weeks may not be sufficient to determine the pharmacological action of these medications [10].

Studies evaluating varying doses of ICS-only therapy are also described in this review [19,24]. In these studies, higher doses of ICS were found to improve asthma in smokers [19,24]. Tomlinson et al. measured four asthma control indicators including ACQ score, lung function (FEV1 and PEF), symptoms and SABA use, to assess ICS response. Parallel groups were assigned beclomethasone 400 µg or beclomethasone 2000 µg [19]. Lung function improvements were observed in nonsmokers prescribed 400 µg; however, no such improvements were reported in smokers prescribed the same dose [19]. Of smokers taking 2000 µg, morning PEF values improved over 12 weeks; however, a greater improvement was noted in nonsmokers receiving this dose. No significant difference in lung function (FEV1 and PEF) was reported between smokers taking 400 and 2000 µg ($p=0.43$) [19]. Regarding symptoms, smokers on lower dose beclomethasone had experienced more exacerbations than nonsmokers by week 12 ($p=0.0067$) [19]. Nonsmokers exhibited a larger improvement in symptoms by week 12 as well [19]. Across both treatment groups, no differences were noted in

symptoms between smokers and nonsmokers; however, smaller improvements in ACQ score did occur in nonsmokers compared to smokers ($p=0.0130$) [19]. Based on changes to multiple asthma control indicators over time, Tomlinson et al. conclude that the use of higher dose ICS-only therapy may provide some benefit to smokers, although it is more apparent that this form of therapy improves asthma in nonsmokers [19]. In a similar study, Telenga et al. evaluated ICS use in three groups: (1) A self-management care group receiving varying doses of fluticasone, (2) Fluticasone 500 µg and (3) Fluticasone 2000 µg. ICS effects were measured using blood eosinophil and neutrophil counts as well as lung function (i.e. FEV1) in never, former and current smokers [24]. Based on smoking status, significant improvements in FEV1 were noted in former ($p=0.011$) and never smokers ($p<0.001$), yet marginal improvements were seen in current smokers ($p=0.058$) [24]. Between treatment groups, differences in FEV1 were insignificant [24]. Based on changes in FEV1, this study concluded that ICS-only therapy, even at higher doses, may be less effective for smokers [24]. Findings from Tomlinson et al. and Telenga et al. offer insight into the value and effectiveness of ICS-only therapy in controlling asthma in smokers. Although four indicators were measured in Tomlinson et al.'s study, researchers relied largely on lung function outcomes to determine the effectiveness of ICS, identifying PEF as the main endpoint under study [19]. In Telenga et al.'s study, although other outcomes were measured, the only guideline-based indicator assessed was lung function as well. In both studies, as based on changes in lung function, ICS-only therapy was shown to offer some therapeutic benefit to smokers although larger improvements were reported in nonsmokers.

Studies of low- and high-dose combination therapy were also included in this review [14]. Schayck et al. (evaluated day symptoms, nighttime awakenings, PEF, SABA use and ACQ score in participants receiving either one or two puffs of budesonide/formoterol (160 µg/4.6 µg) twice a day. Nonsmokers enrolled in this study were shown to benefit from both treatments; however, among smokers ICS response varied. Lung function values were obtained for participants at baseline and showed that FEV1 values were similar across smokers and nonsmokers ($p=0.1817$), however PEF values differed ($p=0.0026$). Across measured indicators, smokers receiving two puffs experienced significant improvements in ACQ, asthma symptoms, SABA use and night-time awakenings compared to smokers using only one puff (Table 2) [14]. Results of this study show the therapeutic benefit provided to smokers using higher doses of combination therapy compared to lower doses of the same drugs. Also, as multiple indicators of control were used to assess asthma in this study, one can conclude that combination medications may improve asthma as based on a comprehensive patient assessment.

Smoking history

Across included studies mean pack years varied, ranging from 0.1 to 36.5 years. A trial comparing outcomes of patients with less than 5 pack years to those with more than

5 years reported that a longer smoking history resulted in a reduced response to ICS as measured by changes in FEV1 [18]. In a similar study, ICS therapy was used for smokers with ≥ 10 pack years; however, the increase in lung function was marginal relative to nonsmoking participants [22]. In included studies of smokers with >20 pack years, ICS-only therapy was found to be ineffective in managing asthma [19,22]. In both of these studies, multiple indicators of asthma control were measured; however, findings across these indicators were consistent with reduced ICS response [19,22]. As evident to these findings, smokers with less pack years may benefit from ICS compared to asthmatics with longer smoking histories. Additional studies on the effectiveness of combination therapy in smokers with >20 pack years may provide insight into effective treatments for patients with longer smoking histories. Also, by incorporating asthma control indicators as outcomes under study, researchers can determine if proposed therapies are improving asthma status as based on guideline recommended best practices.

Limitations of included articles

Several limitations are noted within individual articles included in this review. Across studies the exclusion of patients based on comorbidities were not fully disclosed, however, in RCTs this is a regulatory practice [9]. Comorbid diagnoses have the potential to confound results and impact data collected from patient self-reports such as lung function, symptom days, night-time awakenings and use of SABA [9,27]. Specifically regarding smokers with asthma, the risk of COPD diagnoses increases with age [28]. The presence of COPD may confound results as this potentially comorbid condition presents as obstructive disease in pulmonary function testing. Specifically, the decline in lung function often seen in patients with COPD, may also be observed in patients with asthma [28]. This is important as many studies included in this review rely on lung function, namely FEV1 and/or PEF, as the sole indicator of asthma status. Future studies should describe specific exclusion criteria for patients with comorbid respiratory conditions as well as detail methods used to exclude these patients in trials.

Various diagnostic methods were also found across articles. For example, in one study, asthma status was determined by patient report rather than by clinician-confirmed diagnoses [17]. In this case, patients were asked to answer the question “Do you have asthma?” [17]. This method relied solely on patient report for study inclusion. In future studies, clinical diagnostic measures should be employed to confirm diagnoses rather than confirmation of asthma status by patient self-report.

Although studies utilized asthma control indicators to evaluate ICS effectiveness, studies lacked actual asthma control assessments. By conducting guideline-based assessments and properly classifying patients as well controlled, not well controlled, or very poorly controlled, researchers can determine whether the ICS under study is improving overall asthma control rather than individual indicators. Based on this asthma control classification appropriate asthma pharmacotherapy can be maintained or adjusted [3].

Limitations of this review

Limitations of this review relate to the inclusion and exclusion criteria of the search. Due to the limited availability of intervention-only articles on the effectiveness of ICS therapy for smokers, all articles that met inclusion criteria, regardless of study design, were included in the analysis. Therefore, regarding the results of included articles, the effects of some studies may appear greater than others as all studies did not evaluate ICS response in the same manner. RCTs included in this review report on the efficacy of ICS therapies; however, other studies can only report on improvements in asthma or specific indicators measured. This limitation prohibits authors from comparing results across studies as well as generalizing results to the larger population. Also related to study design, even studies not describing exclusion criteria for comorbid conditions were included (i.e. nonrandomized controlled trials). As age and smoking duration increases, so does the risk of developing tobacco-related respiratory diseases, such as COPD, emphysema and chronic bronchitis [1,27]. Limiting age criteria in future searches may be beneficial in reducing potential for the inclusion of patients with comorbid pulmonary conditions.

The authors searched three databases for purposes of this review. The addition of more databases may have identified more studies however with the inclusion of PubMed as a database, we feel that a substantial number of publications meeting our criteria were identified. Several authors were also contacted to obtain detailed information on methods of diagnosing asthma as well as methods of monitoring adherence in their respective studies. Responses from these authors were not received or contact information listed with the article was no longer current.

Strengths of this review

Few reviews exist on the use of ICS therapy in smokers, and this is the first review to evaluate use of guideline-based methods to monitor the effects of ICS in smokers with asthma. Results reveal that many researchers rely on one indicator, namely lung function, to measure the therapeutic effects of these drugs. However, as previously stated, the evaluation of asthma status should include the assessment of patients as based on multiple indicators as detailed in the asthma clinical guidelines. Without the use of multiple indicators, asthma status may be over or underestimated which may lead to asthma being over or under treated.

This review also exposes a need to include smokers in clinical trials as treatment outcomes for smokers and nonsmokers differ. Because smokers are often excluded from these studies additional research including smokers should be conducted in order to determine the therapeutic effects of various types of ICS in this subpopulation. Findings from clinical trials including smokers may add significantly to asthma guidelines, creating a framework of care for a population whose specific needs have been previously excluded. Findings of this review have the potential to inform new research as well as new guidelines that detail specific treatment recommendations for smokers with asthma.

Conclusion

This review analyzed findings relating to the use of guideline-based indicators to assess the effects of ICS therapy in asthmatic smokers. Observations made in this review expose a need to evaluate the effectiveness of ICS therapy using multiple asthma control indicators. Of studies included in our review, the most common indicator measured was lung function to determine asthma status. Conclusions made based solely on one indicator may lead clinicians to conclude that ICS drugs are ineffective, resulting in treatment with more aggressive therapies. However, our review also reveals that combination therapy may be more effective in improving asthma symptoms in smokers than ICS-only drugs. In prescribing therapies, it is therefore important to follow evidence-based guidelines that can ultimately protect patients. Furthermore, considerations for the treatment of smokers should be included in clinical practice guidelines as it is evident that ICS response in smokers and nonsmokers may differ. Regarding future research, asthma drug efficacy trials should include the recruitment of smokers with varying pack year histories, as they represent a substantial proportion of adult asthmatics who could benefit from treatment. Additionally in studies evaluating asthma drug effects, researchers should perform asthma control assessments in order to classify the level of asthma control in each participant. These classifications will also allow clinicians to determine if current guideline recommendations are sufficient in improving asthma in smokers, or if specialized guidelines should be considered for this subset of patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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