ERJ Express. Published on September 6, 2018 as doi: 10.1183/13993003.00703-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Review

Consequences of long-term OCS therapy and its side effects in severe asthma in adults – A focused review of the impact data in the literature

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Please cite this article as: Volmer T, Effenberger T, Trautner C, *et al*. Consequences of long-term OCS therapy and its side effects in severe asthma in adults – A focused review of the impact data in the literature. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.00703-2018).

Consequences of long-term OCS therapy and its side effects in severe asthma in adults – A focused review of the impact data in the literature

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Background

Asthma is a chronic inflammatory airway disease affecting about 235 million people worldwide [1]. In approximately 4% to 8% of asthma patients symptoms remain uncontrolled and exacerbations occur frequently despite high-intensity treatment, or they need systemic corticosteroid treatment for sustained symptom control [2, 3]. Systemic corticosteroids, usually administered orally, are widely used both intermittently or long-term in this population regardless of side effects that may develop during an extended period of exposure [4], which are associated with a tremendous economic burden [5]. According to data from the Healthcare Cost and Utilization Project, corticosteroids in general were the most common cause of drug-related complications in 2004, accounting for 10% of all drug-related complications and 141,000 hospital stays in the United States [6]. The Global Initiative for Asthma (GINA) guidelines therefore recommend use of oral corticosteroids (OCS) for maintenance therapy only in patients with uncontrolled severe asthma despite treatment with all available controller drugs including biologics if appropriate, and only as low dosed and as short as possible [7]. Most studies investigating the side effects of OCS observed patients receiving this medication for various underlying illnesses, often rheumatoid diseases. An overview of the typical side effects of OCS found in these studies was presented by Schäcke *et al.* [8]. OCS treatment can affect skin, skeleton, muscles, eyes, central nervous system, metabolism, cardiovascular system, immune system, and gastrointestinal system. In these studies, asthma is mostly only one of the possible indications for OCS treatment in the analysed patients. Relatively few data are available from well-described cohorts of patients with severe asthma only. The purpose of this review is to systematically assess the potential side effects of long-term OCS treatment in patients with severe asthma and to compare dosing schemes recommended by the GINA guidelines with published data from studies analysing dose-response relationships.

The role of OCS in severe asthma

Because asthma is a chronic inflammatory airway disease, corticosteroids are a very effective therapy. Consequently, maintenance therapy with inhaled corticosteroids (ICS) is recommended for all asthma patients and mandatory for patients with more than just occasional symptoms (≥ twice a week) [7, 9]. Most patients need additional bronchodilation. Therefore, long-acting beta agonists (LABA) are added, for compliance reasons typically in a fixed combination with ICS for inhalation. Inhalation as an aerosol or powder delivers the corticosteroids to the bronchial and lung tissue, optimising local anti-inflammatory while minimising undesirable systemic effects.

According to GINA, severe asthma is asthma requiring step 4 or 5 treatment, e.g. high dose ICS/LABA ± a third controller, to maintain control or asthma that remains uncontrolled despite this treatment

[7]. It is important to distinguish severe asthma from asthma that is insufficiently controlled due to inappropriate treatment, lack of treatment adherence, psychosocial factors, or insufficiently controlled comorbidities. This definition is in line with the international ERS/ATS guidelines on severe asthma [10].

The majority of patients with severe asthma that is insufficiently controlled by ICS and LABA and additional anti-inflammatory drugs (e.g. leukotriene antagonists) and bronchodilators (e.g. anticholinergics such as tiotropium) will be escalated to treatment with systemic corticosteroids [2, 3]. Systemic application of corticosteroids increases the desired anti-inflammatory effect, while the typical undesired side effects of systemic corticosteroids may co-occur – depending on dose, duration of treatment, and individual susceptibility. Two different uses of OCS in asthma need to be distinguished: OCS as 'controller option' for severe asthma and OCS as short-term treatment of exacerbations. The focus of this article is on the use of OCS as controller therapy in patients with severe asthma.

OCS as controller therapy for severe asthma

In step 5 of national [11] and international [7] guidelines different add-on treatments to ICS+LABA, e.g. tiotropium as well as anti-IgE and anti-IL-5 antibodies are recommended and, as a second-choice option, low dose OCS. This represents a downgrading of the role of OCS by GINA, in line with increasing clinical evidence supporting the use of tiotropium as additional bronchodilator in severe asthma as well as omalizumab in severe allergic asthma and monoclonal antibodies against interleukin-5 in severe eosinophilic asthma: Until 2012, GINA recommended in step 5 the addition of an oral glucocorticosteroid (lowest dose) or anti-IgE treatment in severe allergic asthma on top of step 4 treatment (ICS+LABA) as controller options without giving explicit preference to either [12]. Starting in 2014, the GINA guidelines recommended add-on treatment, e.g. anti-IL-5 and anti-IgE, as the preferred controller choice and low dose OCS as 'other' controller option only [13]. GINA based this recommendation on the substantial side effects of OCS, although it may be effective for some patients [7].

Recommended duration of OCS treatment as a controller option

OCS should be considered a temporary option only. Recommendations by GINA emphasise the need to step down or terminate OCS treatment when it is no longer needed or proves to be ineffective. In most patients, reduction of OCS doses or a step-down trial is indicated and feasible after some time. Any step-down of asthma treatment should be considered a therapeutic trial, with the response evaluated in terms of both symptom control and exacerbation frequency. Several options for stepping down from existing OCS treatment levels are recommended by GINA including slowly

tapering OCS dose, or switching to alternate-day OCS treatment, while continuing treatment with high dose ICS/LABA plus/minus additional controller(s) [7].

Common OCS doses in clinical practice

Systemic corticosteroids are usually administered orally in a wide range of doses, starting at 1 mg [14, 15]. In recent randomized trials of anti-IL-5 antibodies as add-on to the existing maintenance therapy of severe eosinophilic asthma, patients received at baseline daily OCS doses within a range of 5-70 mg. This might be a realistic range of OCS doses that patients with severe asthma receive in many parts of the world [15-17]. European real-life data showed a range of 14.3-26.5 mg [18].

A Summary of Product Characteristics (SmPC) for prednisone defines a low OCS dose as 10-40 mg/day, and a 'very low dose' as 1.5-7.5 mg/day, possibly up to 10 mg/day. This is in line with the recommended daily dose (DDD) defined by the WHO of 10 mg per day. The same SmPC allows a dose of up to 100 mg per day while recommending tapering the dose soon after clinical response and a maintenance dose independent of specific indications, that is as low as possible, usually between 5 and 15 mg of prednisone per day [19]. In what consequences a 'very low dose' or 'low dose' OCS asthma treatment result, was investigated using a systematic literature review.

Methods

A systematic literature search for studies reporting primary data on side effects of maintenance therapy with OCS in adults with asthma was performed in MEDLINE, EMBASE, and the Cochrane Library (see online supplement for more information). Studies focusing on acute short-term therapy for exacerbations were excluded, as the side effects of high dose burst treatment differ from those of long term exposure. Studies in paediatric populations were also excluded, as the side effects of OCS in children are well known and described in comparison to those in adult patients. An additional hand search in the references of sighted publications was performed to complete the results.

Results

The search resulted in 9 publications with studies of 7 large datasets from registers or health insurance claims. The studies by Sweeney *et al.* [14] and Barry *et al.* [20-22] used partly the same dataset. The results of the studies are summarised in Table 1 and Table 2 presented separately by the different organ classes to facilitate the comparison of effect sizes.

Table 1: Summary of results from included studies by OCS dose

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Bone and muscle complications										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Bone muscle	A vs D	2.42	2.29-2.55	sig.	The category muscle and bone contains avascular necrosis, muscle weakness, osteoporosis, back pain, and fractures.
						B vs D	2.28	2.16-2.40	sig.	
						C vs D	1.36	1.16-1.59	sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Bone muscle	A vs C	1.59	1.29-1.96	sig.	The category muscle and bone contains avascular necrosis, muscle weakness, osteoporosis, back pain, and fractures.
						B vs C	1.51	1.25-1.82	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Bone muscle	A vs D	1.89	1.68-2.12	sig.	The category muscle and bone contains avascular necrosis, muscle weakness, osteoporosis, back pain, and fractures.
						B vs D	1.72	1.55-1.92	sig.	
						C vs D	1.09	0.94-1.26	n.sig.	
Daugherty *et al.*, 2018 [25]	N=35,424			N=24,994	Osteoporosis	A vs D	12.61*	10.45-15.21	<0.0001	
						B vs D	6.79*	5.98-7.73	<0.0001	
						C vs D	1.64*	1.51-1.78	<0.0001	
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Osteoporosis	A vs D	1.83	1.50-2.25	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Fractures	A vs D	1.50	1.11-2.04	0.0099	
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Osteoporosis	A vs C	1.73	1.21-2.41	0.0035	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Fractures	A vs C	1.63	1.22-2.14	0.0015	
Adrenal complications										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Adrenal complications	A vs D	40.67	15.12-109.35	sig.	The category adrenal contains cushing's syndrome.
						B vs D	20.95	7.62-57.63	sig.	
						C vs D	3.87	0.93-16.06	n.sig.	
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Poisoning by adrenal corticosteroids	A vs C	12.38	5.36-28.86	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Cardiovascular system										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Cardiovascular	A vs D	1.73	1.57-1.90	sig.	The category cardiovascular contains atrial fibrillation, flutter, hypertension, and myocardial infarction.
						B vs D	1.77	1.62-1.93	sig.	
						C vs D	1.21	0.90-1.62	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Cardiovascular	A vs C	1.96	1.48-2.58	sig.	The category cardiovascular contains atrial fibrillation, flutter, hypertension, and myocardial infarction.
						B vs C	2.12	1.63-2.76	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Cardiovascular	A vs D	2.06	1.76-2.41	sig.	The category cardiovascular contains atrial fibrillation, flutter, hypertension, and myocardial infarction.
						B vs D	2.23	1.93-2.59	sig.	
						C vs D	1.14	0.87-1.48	n.sig.	
Daugherty *et al.*, 2018 [25]	N=35,424			N=24,994	Myocardial infarction	A vs D	2.15*	1.67-2.77	<0.0001	
						B+C vs D	1.25*	1.09-1.43	0.0012	
					Stroke	A-C vs D	1.11*	0.97-1.27	0.1253	
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Hypertension	A vs D	1.29	1.17-1.42	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Hypertension	A vs C	1.49	1.28-1.73	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
Metabolic complications										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Metabolic	A vs D	1.35	1.25-1.45	sig.	The category other contain hyperglycemia, dyslipidemia, obesity, diabetes mellitus, and metabolic syndrome.
						B vs D	1.32	1.23-1.41	sig.	
						C vs D	0.87	0.72-1.07	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Metabolic	A vs C	1.51	1.23-1.85	sig.	The category other contain hyperglycemia, dyslipidemia, obesity, diabetes mellitus, and metabolic syndrome.
						B vs C	1.50	1.25-1.81	sig.	

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Metabolic	A vs D	1.55	1.37-1.75	sig.	The category other contain hyperglycemia, dyslipidemia, obesity, diabetes mellitus, and metabolic syndrome.
						B vs D	1.56	1.38-1.76	sig.	
						C vs D	1.17	0.98-1.40	sig.	
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Diabetes mellitus	A vs D	1.30	1..18-1.44	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Obesity	A vs D	1.17	1.04-1.32	0.0124	
					Lipid disorders	A vs D	0.80	0.73-0.88	<0.0001	
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Diabetes	A vs C	1.12	0.89-1.39	0.3403	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
Eye diseases										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Ocular	A vs D	1.19	1.11-1.28	sig.	The category ocular contains cataracts and glaucoma.
						B vs D	1.09	1.02-1.17	sig.	
						C vs D	0.95	0.84-1.08	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Ocular	A vs C	1.55	1.32-1.83	sig.	The category ocular contains cataracts and glaucoma.
						B vs C	1.29	1.09-1.51	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Ocular	A vs D	2.02	1.78-2.29	sig.	The category ocular contains cataracts and glaucoma.
						B vs D	1.63	1.43-1.87	sig.	
						C vs D	1.33	1.14-1.54	sig.	
Daugherty *et al.*, 2018 [25]	N=35,424			N=24,994	Cataracts	A vs D	3.38*	2.41-4.73	<0.0001	
						B vs D	1.76*	1.52-2.04	<0.0001	
						C vs D	1.07*	1.00-1.15	0.052	
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Glaucoma	A vs D	1.25	0.99-1.58	0.0673	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Cataract	A vs D	1.29	1.06-1.57	0.0117	

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Glaucoma	A vs C	1.38	0.86-2.12	0.1560	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Cataract	A vs C	1.42	1.02-1.93	0.0417	
Psychiatric disorders										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Psychiatric	A vs D	1.74	1.62-1.86	sig.	The category psychiatric contains bipolar disorder, depression, sleep disturbances, and steroid psychosis.
						B vs D	1.73	1.62-1.86	sig.	
						C vs D	1.16	0.95-1.41	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Psychiatric	A vs C	1.28	1.03-1.60	sig.	The category psychiatric contains bipolar disorder, depression, sleep disturbances, and steroid psychosis.
						B vs C	1.35	1.10-1.66	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Psychiatric	A vs D	1.46	1.28-1.66	sig.	The category psychiatric contains bipolar disorder, depression, sleep disturbances, and steroid psychosis.
						B vs D	1.62	1.42-1.84	sig.	
						C vs D	1.40	1.16-1.70	sig.	
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Depression	A vs C	1.07	0.85-1.32	0.5713	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Anxiety	A vs C	1.64	1.33-2.00	<0.0001	
Infections										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Infections	A vs D	2.43	2.17-2.71	sig.	The category infections contains fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection, and bursitis.
						B vs D	2.25	2.11-2.40	sig.	
						C vs D	1.70	1.34-2.16	sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Infections	A vs C	1.91	1.51-2.43	sig.	The category infections contains fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection, and bursitis.
						B vs C	1.72	1.37-2.16	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Infections	A vs D	2.94	2.61-3.33	sig.	The category infections contains fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection, and bursitis.
						B vs D	2.53	2.27-2.82	sig.	
						C vs D	1.56	1.34-1.81	sig.	

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Opportunistic infections	A vs D	4.16	2.34-8.00	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
					Pneumonia	A vs D	3.22	2.84-3.66	<0.0001	
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Infections	A vs C	1.64	1.38-1.95	<0.0001	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
Gastrointestinal complications										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Gastrointestinal	A vs D	1.96	1.84-2.10	sig.	The category gastrointestinal contains nausea, vomiting, gastrointestinal bleeds, ulcers, and dyspepsia.
						B vs D	2.02	1.89-2.15	sig.	
						C vs D	1.18	0.98-1.41	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Gastrointestinal	A vs C	1.81	1.46-2.24	sig.	The category gastrointestinal contains nausea, vomiting, gastrointestinal bleeds, ulcers, and dyspepsia.
						B vs C	1.63	1.34-1.99	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Gastrointestinal	A vs D	2.55	2.28-2.84	sig.	The category gastrointestinal contains nausea, vomiting, gastrointestinal bleeds, ulcers, and dyspepsia.
						B vs D	2.31	2.08-2.56	sig.	
						C vs D	1.50	1.28-1.76	sig.	
Daugherty *et al.*, 2018 [25]	N=35,424			N=24,994	Peptic ulcer	A-C vs D	1.13*	1.00-1.28	0.0486	
Zazzali *et al.*, 2015 [26]	N=3604			N=3604	Peptic ulcer	A vs D	1.14	0.40-3.32	1	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.
Zeiger *et al.*, 2017 [27]	N=782		N=8764		Ulcer disease	A vs C	3.62	1.30-8.66	0.0136	The OR, CI, and p presented in this review were calculated by the SmartStep Data Institute.

Study	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side effect	Compa-rison	OR	CI	p	Comment
Various										
Dalal *et al.*, 2016 [23]	N=12,697			N=12,697	Skin disease	A vs D	1.66	1.51-1.83	sig.	The category skin disease contains bruising, impaired wound healing, striae, and skin thinning. The category other contains bladder cancer, epistaxis, and Non-Hodgkin's lymphoma.
						B vs D	1.42	1.28-1.57	sig.	
						C vs D	1.37	1.18-1.59	sig.	
					Other	A vs D	1.82	1.61-2.05	sig.	
						B vs D	1.77	1.56-2.00	sig.	
						C vs D	1.13	0.88-1.46	n.sig.	
Lefebvre *et al.*, 2015 [24]	N=1630	N=1630	N=368		Other	A vs C	1.23	0.95-1.60	n.sig.	The category other contains bladder cancer, epistaxis, and Non-Hodgkin's lymphoma.
						B vs C	1.36	1.07-1.73	sig.	
Lefebvre *et al.*, 2017 [22]	N=1630	N=1630	N=368	N=26,987	Hemato/onco	A vs D	1.69	1.35-2.12	sig.	The category hemato/onco contains bladder cancer, epistaxis, and Non-Hodgkin's lymphoma.
						B vs D	1.96	1.59-2.41	sig.	
						C vs D	1.58	1.24-2.01	sig.	

* The study by Daugherty *et al.* provided Hazard Ratios (HR) instead of Odds Ratios (OR)
CI: confidence interval; OCS: oral corticosteroids; OR: Odds Ratio; p: p value; sig.: significant; n.sig.: not significant

Table 2: Summary of results from included studies by disease severity

Study	Severe asthma (CSD) A	Severe asthma (NCSD) B	Mild to moderate asthma C	Non asthmatics D	Side effect	Comparison	OR	CI	p
Bone and muscle complications									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Osteopenia	A+B vs C	5.26	3.75-7.37	<0.001
						A+B vs D	6.68	4.28-10.43	<0.001
					Osteoporosis	A+B vs C	5.23	3.97-6.89	<0.001
						A+B vs D	6.53	4.63-9.21	<0.001
					Fractures	A+B vs C	1.54	1.06-2.22	0.022
						A+B vs D	1.65	1.14-2.39	0.007
Sweeney *et al.*, 2016	N=422	N=328			Osteopenia	A vs B	1.15	0.73-1.81	0.36
					Osteoporosis		1.21	0.67-2.17	0.44
					Fractures		3% vs 0.3%[§]		0.007
Adrenal complications									
Sweeney *et al.*, 2016 [14]	N=422	N=328			Cushingoid symptoms	A vs B	6% vs 0.3%[§]		<0.001
					Adrenal insufficiency		3% vs 0.3%[§]		0.010
Cardiovascular system									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Hypertension	A+B vs C	1.35	1.12-1.61	0.001
						A+B vs D	1.76	1.44-2.14	<0.001
					Cardiovascular disease	A+B vs C	1.36	1.02-1.81	0.035
						A+B vs D	1.57	1.14-2.15	0.005
Sweeney *et al.*, 2016	N=422	N=328			Hypertension	A vs B	1.59	1.07-2.37	0.012
					Cardiovascular disease		0.71	0.39-1.30	0.41
Metabolic complications									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Type II diabetes	A+B vs C	1.46	1.11-1.91	0.006
						A+B vs D	1.76	1.30-2.38	<0.001
					Obesity (BMI >30 kg/m^2)	A+B vs C	1.36	1.16-1.59	<0.001
						A+B vs D	2.04	1.74-2.39	<0.001
					Hypercholesterolaemia	A+B vs C	1.15	0.92-1.44	0.21
						A+B vs D	1.61	1.25-2.08	<0.001

Study	Severe asthma (CSD) A	Severe asthma (NCSD) B	Mild to moderate asthma C	Non asthmatics D	Side effect	Comparison	OR	CI	p
Sweeney *et al.*, 2016 [14]	N=422	N=328			NIDDM	A vs B	3.48	1.94-6.26	<0.001
					Obesity (BMI >30 kg/m2)		1.47	1.10-1.97	0.016
					Weight gain		12% vs 1%[§]		<0.001
Eye diseases									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Glaucoma	A+B vs C	1.12	0.75-1.68	0.58
						A+B vs D	1.41	0.89-2.25	0.15
					Cataract	A+B vs C	1.89	1.39-2.56	<0.001
						A+B vs D	2.42	1.70-3.43	<0.001
Sweeney *et al.*, 2016 [14]	N=422	N=328			Glaucoma	A vs B	0.83	0.28-2.50	0.98
					Cataract		6% vs 0%[§]		0.002
Psychiatric disorders									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Psychiatric conditions/anxiety/ Depression	A+B vs C	1.43	1.22-1.69	<0.001
						A+B vs D	1.67	1.42-1.97	<0.001
					Sleep disorders	A+B vs C	1.70	1.13-2.53	0.010
						A+B vs D	2.21	1.46-3.35	<0.001
Sweeney *et al.*, 2016 [14]	N=422	N=328			Depression/anxiety/low mood	A vs B	2.57	1.76-3.76	<0.001
					Sleep disturbance		4% vs 1%[§]		0.003
Gastrointestinal complications									
Sweeney *et al.*, 2016 [14] Barry *et al.*, 2017 [21] Barry *et al.*, 2018 [20]	N=808		N=3975	N=2412	Dyspeptic disorders	A+B vs C	3.99	3.37-4.72	<0.001
						A+B vs D	4.88	4.11-5.79	<0.001
Sweeney *et al.*, 2016	N=422	N=328			Dyspeptic disorders	A vs B	1.96	1.45-2.64	<0.001

Study	Severe asthma (CSD) A	Severe asthma (NCSD) B	Mild to moderate asthma C	Non asthmatics D	Side effect	Comparison	OR	CI	p
Various									
Sweeney *et al.*, 2016 [14]	N=422	N=328			Skin conditions	A vs B	4% vs 0.3%[§]		0.002
					Obstructive sleep apnoea		2.80	1.48-5.29	<0.001

[§] The publication did not provide odd ratios (OR) for side effect with few events. In this review we will provide percentages in these cases instead if a threshold of >1% was reached in any group.

BMI: Body Mass Index; CI: confidence interval; NIDDM: non insulin dependent diabetes mellitus; OCS: oral corticosteroids; OR: Odds Ratio; p: p value

Table 1 and Table 2 show an increased susceptibility of a wide range of investigated side effects after exposure to OCS in comparison to the control groups.

Dose-response relationship

To investigate whether there is a dose-response relationship between long-term treatment with OCS and OCS-related side effects, Dalal *et al.* performed a subgroup analysis based on the extent of OCS exposure (Figure 1 [23]).

The analysis reflects a statistically significant linear relationship between increasing OCS exposure in terms of dose and duration and increasing risk of developing OCS-related complications. Patients taking OCS had a higher risk of complications than patients without OCS exposure, independent of the dose. Infections, bone/muscle diseases and skin diseases were significantly more frequent in patients receiving OCS, even if they had received <5 mg of prednisone-equivalent during the observation period. Patients receiving <5 mg/day also showed an elevated risk of acute complications (OR 1.72). For the 'any OCS-related complications' category, the OR was 2.50. In patients receiving an OCS dose ≥5 mg/day, there was a statistically significant increase in the odds of experiencing acute and chronic complications, with reported ORs for infections of 2.25 (2.43 for >10 mg) and for bone/muscle disease of 2.28 (2.42 for >10 mg).

In patients with severe asthma who received >5 mg OCS per day, health care resource utilisation was also increased, with ORs for inpatient visits of 2.40 (3.37 for >10 mg) and for emergency room visits of 1.78 (2.17 for >10 mg). Consequently, the costs per patient of OCS-related complications increased relative to no exposure, with additional annual costs of $2,670, $4,639, and $9,162 for low (<5 mg/day), medium (5-10 mg/day, and high dose (>10 mg/day) OCS treatment, respectively [23]. In a British study, the estimated direct health care treatment costs from a National Health Service perspective were 43% higher for patients on maintenance OCS than for those not receiving maintenance OCS [28].

The Lefebvre study showed similar results, with a significant dose-response relationship found for side effects in patients with severe asthma who received OCS [24]. Infections as well as gastrointestinal, bone and muscle, cardiovascular, metabolic, psychiatric, and ocular complications were significantly more frequent in patients with asthma receiving an OCS treatment of >6 mg/day than in patients receiving <6 mg/day. Patients receiving >12 mg/day showed the same pattern as those receiving 6-12 mg/day, but in most cases with a numerically higher risk of OCS-related complications.

The study by Curtis *et al.* surveyed the use of OCS by patients, of which 12% had asthma, and patient-reported adverse events [29]. The study showed that the proportion of patients reporting side effects of OCS as 'bothersome' or 'very bothersome' raised with increasing cumulative dose. Regular treatment with 5 mg prednisolone-equivalent/day for one year already resulted in an increase in adverse events of about 40% for mood problems, 45% for sleep problems, 40% for skin bruising and 60% for weight gain, and in various other adverse events such as cataracts (10%), high blood sugar (5%) and bone fractures (10%). If >12.5 mg are ingested daily, the frequencies of adverse events, such as mood problems (55%), sleep problems (60%), weight gain (75%), cataracts (15%), and bone fractures (15%), were even higher. It was concluded that the prevalence of 8 commonly attributed self-reported corticosteroid-associated AEs was significantly associated with increasing average corticosteroid dose in a dose-dependent fashion [29].

Quality of life

The influence of OCS on quality of life (QoL) is a multi-faceted topic. At a first glance it seems obvious that patients with severe uncontrolled asthma benefit initially from long-term treatment with OCS due to better asthma control. On the other hand, the multitude of side effects developing over time as a consequence of OCS therapy make improvements in QoL at least questionable [30]. Newer treatments with a 'steroid-sparing' effect proved to be associated with a reduction in corticoid exposure and a simultaneous rise in QoL [16, 31-35]. A mere reduction of OCS is not responsible, as a trial with tapering the dose of OCS while maintaining asthma control - without medication with a steroid-sparing effect - showed that despite the dose reduction of OCS no significant impact on QoL [36]. In the BTS Registry study, quality of life scores were significantly better in the non-corticosteroid-dependent group, although many values (44-46%) were missing [14]. Those partly contradictory results can be explained by the fact that the currently available scales for the assessment of QoL in clinical trials are insufficient for measuring the treatment burden of long-term therapy with OCS [37], and that most steroid-sparing interventions in asthma have an impact on QoL independent of their steroid-sparing potential. Furthermore, the perception of treatment burden may not be adequately measured by commonly used tools for the assessment of QoL as patients could adapt to the chronic use of OCS. For a final assessment of the relationship between long-term treatment with OCS and QoL in asthma patients, development of more sensitive, valid and reliable asthma-specific scales for determination of the treatment burden is necessary.

Discussion

The results of this literature overview support the recommendation by GINA [7] and other asthma guidelines [38] to increase asthma treatment intensity with inhaled drugs such as ICS, LABAs, tiotropium and monoclonal antibodies (e.g. anti-IgE, anti-IL-5) before considering OCS long-term-use.

All long-term OCS therapies independent of the dose have been reported to elevate the risk of comorbidity and complications. Even 'low' doses of OCS - according to guidelines – are leading to complications, as described to the analysed literature. If OCS are used following the guidelines, they should be given as maintenance therapy in the lowest possible dose and as short as possible. The results of the review highlight that a comprehensive look into OCS long-term safety is urgently warranted as part of clinical management (not only) in severe asthma. It also has a cost component, shown for instance in the OPCRD dataset. The health economic impact of severe asthma, showing mean annual total costs of £ 560 - £ 1324 for non-asthmatic patients compared to £ 978 - £ 2072 for mild/moderate and £ 2603 - £ 4533 for severe asthma [21]. Lefebvre *et al.* calculated the cost for patients with low, medium, and high dose intensity were $678, $1181, and $2140 higher than those of OCS non-users due to OCS-related complications [22]. Another important conclusion of our literature review is that clinicians ought to pay high attention to prevent OCS side effects (e.g. substitution with calcium, vitamin D, recommend physical exercise, etc.), as they occur more consistently, widely and costly as previously thought.

This review is limited to adult patients and can therefore not be generalized to paediatric populations. Also, a purely systematic literature search seemed not to be appropriate to better capture the diverse nature of the study designs. As publications retrieved by hand search were also included in the review, a total of 7 datasets and 9 publications were finally consulted to summarize the effects of OCS treatment-related side effects in asthmatic patients.

The study by Dalal *et al.* based on US claims data from 2 Truven Health MarketScan Research databases provided data on the side effects of OCS in a large cohort of patients with severe asthma [23], showing that the risk of corticosteroid-related complications increases with increasing dose of OCS. The findings were confirmed in the studies by Lefebvre *et al.*, who based their research on Medicaid claims data in the US but also used a longitudinal observational cohort study design [22, 24]. Zazzali *et al.* used US commercial health care claims in a matched cohort study [26] and Zeiger *et al.* presented administrative pharmacy and health care utilization data gathered from the Kaiser Permanente Southern California Research Data Warehouse in a retrospective observational cohort study [27]. All of the above data sources would have been missed by focussing on randomized evidence from clinical trials only.

Limitations of the above data sources result from the typically reported challenges well known for claims data studies: conversion of claims into unique visits, identification of incomplete claims data, categorization of providers and locations of service, and selecting the most useful measures of utilisation and expenditures [39]. The study by Daugherty *et al.* was also longitudinal in design but did not use claims data. Instead, the study was based on the UK Clinical Practice Research Datalink (CPRD) Database [25].

Unlike the longitudinal studies, the studies by Sweeney *et al* [14] and Barry et al. [20, 21] were cross-sectional in design, so that the point prevalence can be measured, but reliable incidence rates are not available. In these two studies, the risks of complications for patients with severe asthma compared with non-asthmatic controls seem to be greater than those of patients with mild/moderate asthma. Higher risks of concomitant disease in patients with asthma than in people without asthma may also contribute to the above findings. The significantly higher prevalence of comorbidities like diabetes and hypertension in asthmatics versus non-asthmatics recently reported by Su *et al.* [40] may also explain the increased risk of chronic kidney disease found in patients with severe asthma by Sweeney *et al.* as diabetes and hypertension have a negative impact on kidney function. An increase in depression, anxiety, mood disorders and sleep disorders may in part be explained by an increased severity of the disease. The same is true for the detrimental impact on quality of life. All these limitations suggest that some of the apparently increased risks of patients with severe asthma may in fact be due to the severity of the disease – and not only the detrimental effects of long-term OCS treatment.

Taken together, all the identified studies demonstrate a substantially increased risk for 'typical' steroid-induced side effects in patients with severe asthma who take OCS long-term. In line with these findings, the GINA guidelines recommend counselling about potential side effects, regular checks of blood pressure as well as monitoring for risk of corticosteroid-induced osteoporosis in patients with asthma who receive OCS as maintenance therapy and appropriate prevention of osteoporosis for patients expected to be treated for ≥3 months [7].

Comparison of the OCS doses received by patients in included studies with the recommended GINA dose for treatment of severe asthma revealed that the GINA recommendation (≤7.5 mg/day) was already regarded as medium exposure [22-24] or as high exposure [25, 27].

A different approach was used by Zazzali *et al.*: High OCS use was defined as more than 30 days of OCS supply per year resulting in a median daily dose of about 3.5 mg/day in the included patients [26]. This is comparable with the low dose groups defined by Dala *et al.* and Lefebvre *et al.* [22-24].

Patients with severe asthma in the BTS Registry took on average 15 mg/day OCS [14]. Obviously, most patients with severe asthma in the BTS Registry therefore received much more than the recommended GINA dose of ≤7.5 mg/day [14]. Even most patients in the comparator group most likely received the equivalent of an average daily dose between 1 and 5 mg per day. To interpret the results of the BTS study, two facts need to be considered: The doses taken by the patients with severe asthma were considerably higher than those taken by the patients in the other included studies. However, whereas the comparator groups in the OPCRD (non-asthma) and the studies by Dalal *et al.*, Daugherty *et al.*, Lefebvre *et al.*, and Zazzali *et al.* [22-26] were not exposed to any OCS, the comparator group in the BTS study received a considerable average dose due to rescue medications during periods of exacerbation.

Conclusion

Several independent studies demonstrate that the exposure of side effects of long-term OCS treatment of severe asthma is associated with the level of the daily dose used. Side effect severity of chronic OCS exposure presenting itself as continuum starting even at very low doses below 5 mg per day. We could not find a well-founded threshold for side effects of OCS or a dosing window for a 'safe' long-term use. On the basis of these findings, the advantage of a better asthma control with OCS must be thoroughly weighed against the risk of side effects. Effective corticosteroid-sparing strategies must be used to reduce side-effects. If OCS treatment is needed, one should aim at short-term use with the lowest effective dose and start tapering as soon as possible until OCS therapy is terminated.

The GINA guidelines now recommend (steroid sparing therapies like) omalizumab, benralizumab, reslizumab and mepolizumab as a preferred treatment choice over the use of OCS. And, the German guideline already recommends to initiate an OCS therapy only after all other step 5 treatments (tiotropium, anti-IgE, or anti-IL-5) have failed or are not suitable because of side effects [11]. Severe asthma patients may benefit from phenotyping their disease in terms of disease control and treatment-related adverse events. [7]

Funding

This research was partly funded through a restricted grant from Teva.

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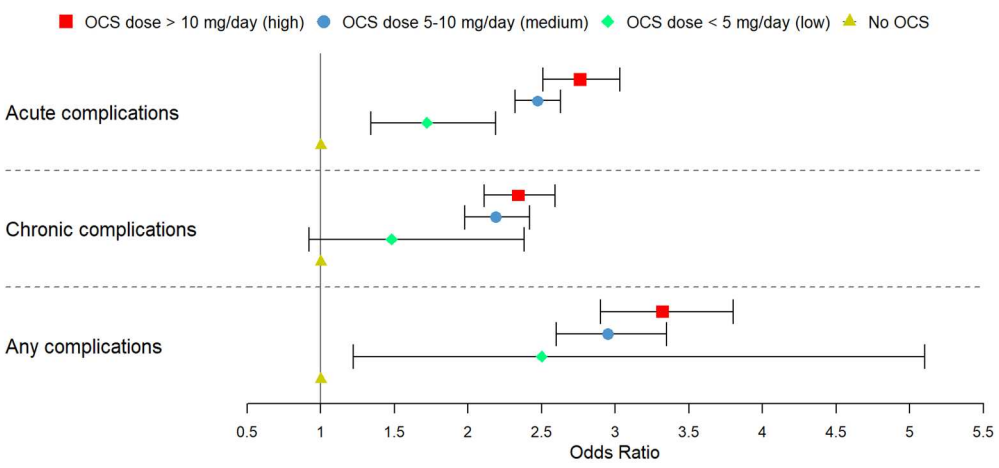

Figure 1: Risk of developing OCS-related complications by different OCS dose exposures. OCS doses < 5 mg/day are considered as low, ≥ 5-10 mg/day as medium and > 10 mg/day as high doses [23]. An Odds Ratio (OR) > 1 describes a higher risk for developing OCS-related side effects. OCS = oral corticosteroids

Material and Methods

In order to obtain relevant publications on long term asthma treatment with oral corticosteroids a systematic literature search in the databases MEDLINE, EMBASE, INAHTA, NHS EED, DARE, and the Cochrane library was conducted. The original search was done in 2016 and was updated in 2018. The search strategy consisted of 3 separate blocks, one block each for intervention, indication, and a filter for treatment-related publications (Table S1, Table 2, Table S3, and Table S4). Only studies reporting primary data on side effects of long term oral corticosteroid exposure in adult asthma patients were included. Because of the broad search, the time frame of the search was limited to the last 5 years (original search in 2016). To ensure the equal consideration of older publications reference lists of all included publications were screened for additional relevant publications. In the first pass, titles and abstracts of all hits from the literature search were analyzed for eligibility. Potential relevant hits were the read as full text (Figure S1). Publications with other indications than asthma or short term use of corticosteroids as topic were excluded as well as publications focusing on special populations like children or pregnant women.

Table S1: Search strategy for MEDLINE

Name of database	MEDLINE	
Search interface	PubMed	
Date of the search	28.05.2018	
Time periode	From 19.01.2011	
Filter	No filter	
Line	Search	Hits
#1	system*[tiab] AND (corticosteroid*[tiab] OR glucocorticoid*[tiab])	34031
#2	OCS[tiab] OR "oral corticosteroid*"[tiab]	7471
#3	"oral glucocorticoid*"[tiab]	265
#4	#1 OR #2 OR #3	41350
#5	asthma[tiab]	134977
#6	Asthma[Mesh]	119318
#7	#5 OR #6	160618
#8	treat*[tiab] OR manage*[tiab] OR therap*[tiab]	6673542
#9	#4 AND #7 AND #10	3066
#10	#9 Publication date from 2011/01/19	1099

Table 2: Search strategy for EMBASE

Name of database	EMBASE
Search interface	embase.com
Date of the search	28.05.2018
Time periode	From 2011
Filter	No filter

Line	Search	Hits
#1	system*:ti,ab AND (corticosteroid*:ti,ab OR glucocorticoid*:ti,ab)	49279
#2	OCS:ti,ab or "oral corticosteroid*":ti,ab	11900
#3	"oral glucocorticoid*":ti,ab	1053
#4	#1 or #2 or #3	60281
#5	MeSH descriptor: [Asthma] explode all trees	242460
#6	asthma:ti,ab	192659
#7	#5 or #6	268487
#8	treat*:ti,ab or manage*:ti,ab or therap*:ti,ab	8887658
#9	#4 and #7 and #8	6350
#10	#9 Publication Year from 2011	3149

Table S3: Search strategy for Cochrane Library

Name of database	Cochrane Library
Search interface	Cochrane Library
Date of the search	28.05.2018
Time periode	From 19.01.2011
Filter	No filter

Line	Search	Hits
#1	system*:ti,ab AND (corticosteroid*:ti,ab OR glucocorticoid*:ti,ab)	2962
#2	OCS:ti,ab or "oral corticosteroid*":ti,ab	1141
#3	"oral glucocorticoid*":ti,ab	125
#4	#1 or #2 or #3	4009
#5	MeSH descriptor: [Asthma] explode all trees	10310
#6	asthma:ti,ab	21802
#7	#5 or #6	23475
#8	treat*:ti,ab or manage*:ti,ab or therap*:ti,ab	630589
#9	#4 and #7 and #8	947
#10	#9 Publication Year from 2011	416

All Results	416
Cochrane Reviews	60
All	60
Review	58
Protocol	2
Other Reviews	2
Trials	354
Methods Studies	0
Technology Assessments	0
Economic Evaluations	0
Cochrane Groups	0

Table S4: Search strategy for HTA databases

Name of database	DARE, INAHTA, NHS EED
Search interface	DIMDI
Date of the search	28.05.2018
Time periode	From 2011
Filter	No filter

Line	Search	Hits
#1	(system* AND (corticosteroid* OR glucocorticoid)) IN DARE, NHSEED, HTA FROM 2011 TO 2018	348
#2	("oral glucocorticoid*") IN DARE, NHSEED, HTA FROM 2011 TO 2018	4
#3	(OCS OR "oral corticosteroid*") IN DARE, NHSEED, HTA FROM 2011 TO 2018	39
#4	#1 or #2 or #3	361
#5	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES	676
#6	(asthma) IN DARE, NHSEED, HTA FROM 2011 TO 2018	424
#7	#5 or #6	849
#8	(treat* OR manage* OR therap*) IN DARE, NHSEED, HTA FROM 2011 TO 2018	28719
#9	#4 AND #7 AND #8	72

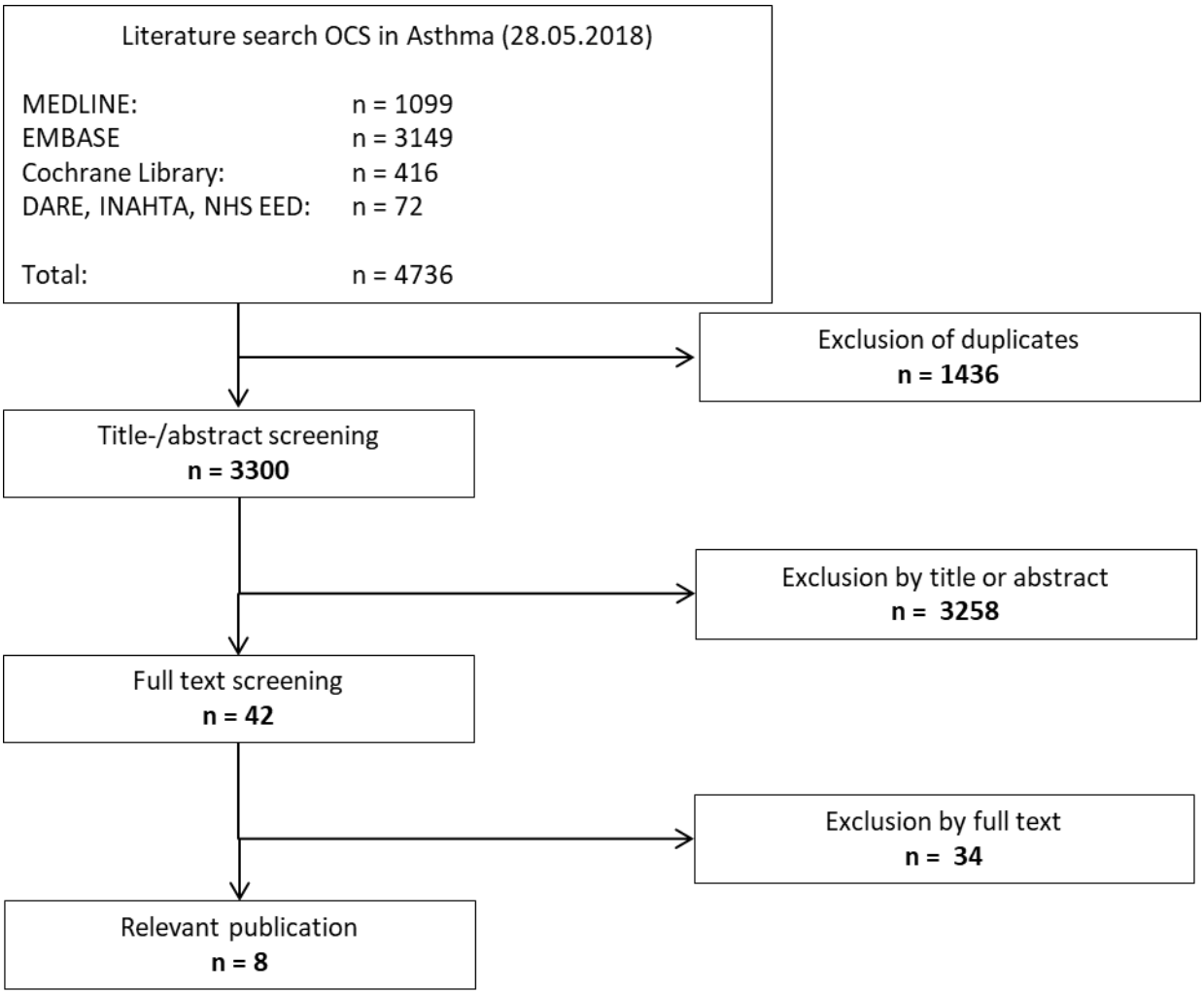

Figure S1: Search flow of the systematic literature search

Overall, the literature search resulted in 4738 hits, of which 1436 publications were duplicates. After title and abstract screening 42 potentially relevant publications remained for a full text review, in which 8 publications were included (Table S5). Because of the limited number of results an additional hand search was performed and 1 additional study was included.

Table S5: List of included publications

No.	Citation
Identified by systematic literature search	
1	Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respiratory research* 2017: 18(1): 129.
2	Barry LE, O'Neill C, Patterson C, Sweeney J, Price D, Heaney LG. Age and Sex Associations with Systemic Corticosteroid-Induced Morbidity in Asthma. *The journal of allergy and clinical immunology In practice* 2018.
3	Daugherty J, Lin X, Baxter R, Suruki R, Bradford E. The impact of long-term systemic glucocorticoid use in severe asthma: A UK retrospective cohort analysis. *Journal of Asthma* 2017: 1-8.

4	Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, Albers F, Yancey S, Ortega H, Forshag M, Lin X, Dalal AA. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. The Journal of allergy and clinical immunology 2015: 136: 1488-1495.
5	Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, Albers F, Yancey S, Ortega H, Forshag M, Lin X, Dalal AA. Burden of systemic glucocorticoid-related complications in severe asthma. *Current medical research and opinion* 2017: 33(1): 57-65.
6	Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, Chaudhuri R, Price D, Brightling CE, Heaney LG. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016: 71(4): 339-346.
7	Zazzali JL, Broder MS, Omachi TA, Chang E, Sun GH, Raimundo K. Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use. Allergy and Asthma Proceedings 2015: 36(4): 268-274.
8	Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Tran TN. Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma. Journal of Allergy and Clinical Immunology: In Practice 2017: 5(4): 1050-1060.e1059.
Identified by hand search	
9	Dalal AA, Duh MS, Gozalo L, Robitaille MN, Albers F, Yancey S, Ortega H, Forshag M, Lin X, Lefebvre P. Dose-Response Relationship Between Long-Term Systemic Corticosteroid Use and Related Complications in Patients with Severe Asthma. Journal of managed care & specialty pharmacy 2016: 22(7): 833-847.