Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature

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ABSTRACT This review provides an overview of the role of long-term treatment of severe asthma with oral corticosteroids (OCS) and its associated side-effects in adults. It is based on a systematic literature search conducted in MEDLINE, Embase and the Cochrane Library to identify relevant studies. After a short overview of severe asthma and its treatment we present studies showing a dose–response relationship in asthmatic patients treated with OCS and then consider by organ systems the undesired effects demonstrated in clinical and epidemiological studies in patients with OCS-dependent asthma. It was found that the risk of developing various OCS-related complications, including infections, diabetes and osteoporosis as well as psychiatric disorders, was higher for patients with long-term exposure to OCS compared with control groups. In addition, studies showed a significant increase in healthcare resource utilisation due to OCS treatment. Therefore, it is incumbent on every clinician to carefully weigh the potential benefit of preventing loss of asthma control against this risk before opting to prescribe long-term OCS therapy. Effective corticosteroid-sparing strategies must be used and should aim at short-term use with the lowest effective dose and start tapering as soon as possible until OCS therapy is terminated.

Background

Asthma is a chronic inflammatory airway disease affecting ~235 million people worldwide [1]. In ~4–8% 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 and 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 [6], 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 USA. 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-term 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 patients analysed. 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 (more than twice a week) [7, 9]. Most patients need additional bronchodilation. Therefore, long-acting β-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 effects, while minimising undesirable systemic effects.

According to GINA, severe asthma is asthma that requires step 4 or 5 treatment, e.g. high-dose ICS+LABA with or without 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 European Respiratory Society/American Thoracic Society [10] guidelines on severe asthma.

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: as a "controller option" for severe asthma, and 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-interleukin (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 IL-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 they 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 with or without 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 randomised trials of anti-IL-5 antibodies as an 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 for prednisone defines a low OCS dose as 10–40 $mg \cdot day^{-1}$, and a "very low dose" as 1.5–7.5 $mg \cdot day^{-1}$, possibly up to 10 $mg \cdot day^{-1}$. This is in line with the defined daily dose recommended by the World Health Organization of 10 mg per day. The same summary of product characteristics 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 5–15 $mg \cdot day^{-1}$ of prednisone [19]. The consequences resulting from "very low dose" or "low dose" OCS asthma treatment 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 (online supplementary material). 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. In addition, studies in paediatric populations were 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 of the references of cited publications was performed to complete the results.

Results

The search resulted in nine publications with studies of seven large datasets from registers or health insurance claims. The studies by SWEENEY et al. [14] and BARRY and co-workers [20, 21] used partly the same dataset. The results of the studies are summarised in tables 1 and 2 presented separately by the different organ classes to facilitate the comparison of effect sizes.

Tables 1 and 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. [23] performed a subgroup analysis based on the extent of OCS exposure (figure 1).

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. In addition, patients receiving <5 $mg \cdot day^{-1}$ showed an elevated risk of acute complications (OR 1.72). For the "any OCS-related complications" category, the odds ratio was 2.50. In patients receiving an OCS dose ⩾5 $mg \cdot day^{-1}$, there was a statistically significant increase in the odds of experiencing acute and chronic complications, with reported odds ratios 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, healthcare resource utilisation was increased, with odds ratios 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 USD 2670, USD 4639 and USD 9162 for low- (<5 $mg \cdot day^{-1}$),

TABLE 1 Summary of results from included studies by oral corticosteroid (OCS) dose

First author, year [ref.]	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side-effect	Comparison	OR (95% CI)	p-value	Comment
Bone and muscle complications									
DALAL, 2016 [23]		12697		12697	Bone, muscle	A versus D	2.42 (2.29–2.55)	Sig.	The category muscle and bone includes avascular necrosis, muscle weakness, osteoporosis, back pain and fractures
						B versus D	2.28 (2.16–2.40)	Sig.	
						C versus D	1.36 (1.16–1.59)	Sig.	
LEFEBVRE, 2015 [24]	1630	1630	368		Bone, muscle	A versus C	1.59 (1.29–1.96)	Sig.	The category muscle and bone includes avascular necrosis, muscle weakness, osteoporosis, back pain and fractures
						B versus C	1.51 (1.25–1.82)	Sig.	
LEFEBVRE, 2017 [22]	1630	1630	368	26987	Bone, muscle	A versus D	1.89 (1.68–2.12)	Sig.	The category muscle and bone includes avascular necrosis, muscle weakness, osteoporosis, back pain and fractures
						B versus D	1.72 (1.55–1.92)	Sig.	
						C versus D	1.09 (0.94–1.26)	NS	
DAUGHERTY, 2018 [25]		35424		24994	Osteoporosis	A versus D	12.61[#] (10.45–15.21)	<0.0001	
						B versus D	6.79[#] (5.98–7.73)	<0.0001	
						C versus D	1.64[#] (1.51–1.78)	<0.0001	
ZAZZALI, 2015 [26]	3604			3604	Osteoporosis	A versus D	1.83 (1.50–2.25)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Fractures	A versus D	1.50 (1.11–2.04)	0.0099	
ZEIGER, 2017 [27]	782		8764		Osteoporosis	A versus C	1.73 (1.21–2.41)	0.0035	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Fractures	A versus C	1.63 (1.22–2.14)	0.0015	
Adrenal complications									
DALAL, 2016 [23]		12697		12697	Adrenal complications	A versus D	40.67 (15.12–109.35)	Sig.	The category adrenal includes Cushing's syndrome
						B versus D	20.95 (7.62–57.63)	Sig.	
						C versus D	3.87 (0.93–16.06)	NS	
ZEIGER, 2017 [27]	782		8764		Poisoning by adrenal corticosteroids	A versus C	12.38 (5.36–28.86)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
Cardiovascular system									
DALAL, 2016 [23]		12697		12697	Cardiovascular	A versus D	1.73 (1.57–1.90)	Sig.	The category cardiovascular includes atrial fibrillation, flutter, hypertension, and myocardial infarction
						B versus D	1.77 (1.62–1.93)	Sig.	
						C versus D	1.21 (0.90–1.62)	NS	
LEFEBVRE, 2015 [24]	1630	1630	368		Cardiovascular	A versus C	1.96 (1.48–2.58)	Sig.	The category cardiovascular includes atrial fibrillation, flutter, hypertension, and myocardial infarction
						B versus C	2.12 (1.63–2.76)	Sig.	
LEFEBVRE, 2017 [22]	1630	1630	368	26987	Cardiovascular	A versus D	2.06 (1.76–2.41)	Sig.	The category cardiovascular includes atrial fibrillation, flutter, hypertension, and myocardial infarction
						B versus D	2.23 (1.93–2.59)	Sig.	
						C versus D	1.14 (0.87–1.48)	NS	
DAUGHERTY, 2018 [25]		35424		24994	Myocardial infarction	A versus D	2.15[#] (1.67–2.77)	<0.0001	
						B+C versus D	1.25[#] (1.09–1.43)	0.0012	
					Stroke	A-C versus D	1.11[#] (0.97–1.27)	0.1253	
ZAZZALI, 2015 [26]	3604			3604	Hypertension	A versus D	1.29 (1.17–1.42)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
ZEIGER, 2017 [27]	782		8764		Hypertension	A versus C	1.49 (1.28–1.73)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute

TABLE 1 Continued									
First author, year [ref.]	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side-effect	Comparison	OR (95% CI)	p-value	Comment
Metabolic complications									
Dalal, 2016 [23]		12697		12697	Metabolic	A versus D	1.35 (1.25–1.45)	Sig.	The category other includes hyperglycaemia, dyslipidaemia, obesity, diabetes mellitus and metabolic syndrome
						B versus D	1.32 (1.23–1.41)	Sig.	
						C versus D	0.87 (0.72–1.07)	NS	
Lefebvre, 2015 [24]	1630	1630	368		Metabolic	A versus C	1.51 (1.23–1.85)	Sig.	The category other includes hyperglycaemia, dyslipidaemia, obesity, diabetes mellitus and metabolic syndrome
						B versus C	1.50 (1.25–1.81)	Sig.	
Lefebvre, 2017 [22]	1630	1630	368	26987	Metabolic	A versus D	1.55 (1.37–1.75)	Sig.	The category other includes hyperglycaemia, dyslipidaemia, obesity, diabetes mellitus and metabolic syndrome
						B versus D	1.56 (1.38–1.76)	Sig.	
						C versus D	1.17 (0.98–1.40)	Sig.	
Zazzali, 2015 [26]	3604			3604	Diabetes mellitus	A versus D	1.30 (1.18–1.44)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Obesity	A versus D	1.17 (1.04–1.32)	0.0124	
					Lipid disorders	A versus D	0.80 (0.73–0.88)	<0.0001	
Zeiger, 2017 [27]	782		8764		Diabetes	A versus C	1.12 (0.89–1.39)	0.3403	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
Eye diseases									
Dalal, 2016 [23]		12697		12697	Ocular	A versus D	1.19 (1.11–1.28)	Sig.	The category ocular includes cataracts and glaucoma
						B versus D	1.09 (1.02–1.17)	Sig.	
						C versus D	0.95 (0.84–1.08)	NS	
Lefebvre, 2015 [24]	1630	1630	368		Ocular	A versus C	1.55 (1.32–1.83)	Sig.	The category ocular includes cataracts and glaucoma
						B versus C	1.29 (1.09–1.51)	Sig.	
Lefebvre, 2017 [22]	1630	1630	368	26987	Ocular	A versus D	2.02 (1.78–2.29)	Sig.	The category ocular includes cataracts and glaucoma
						B versus D	1.63 (1.43–1.87)	Sig.	
						C versus D	1.33 (1.14–1.54)	Sig.	
Daugherty, 2018 [25]		35424		24994	Cataracts	A versus D	3.38[#] (2.41–4.73)	<0.0001	
						B versus D	1.76[#] (1.52–2.04)	<0.0001	
						C versus D	1.07[#] (1.00–1.15)	0.052	
Zazzali, 2015 [26]	3604			3604	Glaucoma	A versus D	1.25 (0.99–1.58)	0.0673	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Cataracts	A versus D	1.29 (1.06–1.57)	0.0117	
Zeiger, 2017 [27]	782		8764		Glaucoma	A versus C	1.38 (0.86–2.12)	0.1560	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Cataracts	A versus C	1.42 (1.02–1.93)	0.0417	
Psychiatric disorders									
Dalal, 2016 [23]		12697		12697	Psychiatric	A versus D	1.74 (1.62–1.86)	Sig.	The category psychiatric includes bipolar disorder, depression, sleep disturbances and steroid psychosis
						B versus D	1.73 (1.62–1.86)	Sig.	
						C versus D	1.16 (0.95–1.41)	NS	
Lefebvre, 2015 [24]	1630	1630	368		Psychiatric	A versus C	1.28 (1.03–1.60)	Sig.	The category psychiatric includes bipolar disorder, depression, sleep disturbances and steroid psychosis
						B versus C	1.35 (1.10–1.66)	Sig.	
Lefebvre, 2017 [22]	1630	1630	368	26987	Psychiatric	A versus D	1.46 (1.28–1.66)	Sig.	The category psychiatric includes bipolar disorder, depression, sleep disturbances and steroid psychosis
						B versus D	1.62 (1.42–1.84)	Sig.	
						C versus D	1.40 (1.16–1.70)	Sig.	
Zeiger, 2017 [27]	782		8764		Depression	A versus C	1.07 (0.85–1.32)	0.5713	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Anxiety	A versus C	1.64 (1.33–2.00)	<0.0001	

Continued

TABLE 1 Continued

First author, year [ref.]	High OCS A	Medium OCS B	Low OCS C	No OCS D	Side-effect	Comparison	OR (95% CI)	p-value	Comment
Infections									
DALAL, 2016 [23]		12697		12697	Infections	A versus D	2.43 (2.17–2.71)	Sig.	The category infections includes fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection and bursitis
						B versus D	2.25 (2.11–2.40)	Sig.	
						C versus D	1.70 (1.34–2.16)	Sig.	
LEFEBVRE, 2015 [24]	1630	1630	368		Infections	A versus C	1.91 (1.51–2.43)	Sig.	The category infections includes fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection and bursitis
						B versus C	1.72 (1.37–2.16)	Sig.	
LEFEBVRE, 2017 [22]	1630	1630	368	26987	Infections	A versus D	2.94 (2.61–3.33)	Sig.	The category infections includes fungal infections, pneumonia, sepsis, tuberculosis, urinary tract infection, varicella infection and bursitis
						B versus D	2.53 (2.27–2.82)	Sig.	
						C versus D	1.56 (1.34–1.81)	Sig.	
ZAZZALI, 2015 [26]	3604			3604	Opportunistic infections	A versus D	4.16 (2.34–8.00)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
					Pneumonia	A versus D	3.22 (2.84–3.66)	<0.0001	
ZEIGER, 2017 [27]	782		8764		Infections	A versus C	1.64 (1.38–1.95)	<0.0001	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
Gastrointestinal complications									
DALAL, 2016 [23]		12697		12697	Gastrointestinal	A versus D	1.96 (1.84–2.10)	Sig.	The category gastrointestinal includes nausea, vomiting, gastrointestinal bleeds, ulcers and dyspepsia
						B versus D	2.02 (1.89–2.15)	Sig.	
						C versus D	1.18 (0.98–1.41)	NS	
LEFEBVRE, 2015 [24]	1630	1630	368		Gastrointestinal	A versus C	1.81 (1.46–2.24)	Sig.	The category gastrointestinal includes nausea, vomiting, gastrointestinal bleeds, ulcers and dyspepsia
						B versus C	1.63 (1.34–1.99)	Sig.	
LEFEBVRE, 2017 [22]	1630	1630	368	26987	Gastrointestinal	A versus D	2.55 (2.28–2.84)	Sig.	The category gastrointestinal includes nausea, vomiting, gastrointestinal bleeds, ulcers and dyspepsia
						B versus D	2.31 (2.08–2.56)	Sig.	
						C versus D	1.50 (1.28–1.76)	Sig.	
DAUGHERTY, 2018 [25]		35424		24994	Peptic ulcer	A-C versus D	1.13[#] (1.00–1.28)	0.0486	
ZAZZALI, 2015 [26]	3604			3604	Peptic ulcer	A versus D	1.14 (0.40–3.32)	1	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
ZEIGER, 2017 [27]	782		8764		Ulcer disease	A versus C	3.62 (1.30–8.66)	0.0136	The odds ratios, confidence intervals and p-values presented in this review were calculated by the SmartStep Data Institute
Various									
DALAL, 2016 [23]		12697		12697	Skin disease	A versus D	1.66 (1.51–1.83)	Sig.	The category skin disease includes bruising, impaired wound healing, striae and skin thinning
						B versus D	1.42 (1.28–1.57)	Sig.	
						C versus D	1.37 (1.18–1.59)	Sig.	
					Other	A versus D	1.82 (1.61–2.05)	Sig.	The category other includes bladder cancer, epistaxis and non-Hodgkin's lymphoma
						B versus D	1.77 (1.56–2.00)	Sig.	
						C versus D	1.13 (0.88–1.46)	NS	
LEFEBVRE, 2015 [24]	1630	1630	368		Other	A versus C	1.23 (0.95–1.60)	NS	The category other includes bladder cancer, epistaxis and non-Hodgkin's lymphoma
						B versus C	1.36 (1.07–1.73)	Sig.	
LEFEBVRE, 2017 [22]	1630	1630	368	26987	Haematology/oncology	A versus D	1.69 (1.35–2.12)	Sig.	The category haematology/oncology includes bladder cancer, epistaxis and non-Hodgkin's lymphoma
						B versus D	1.96 (1.59–2.41)	Sig.	
						C versus D	1.58 (1.24–2.01)	Sig.	

Data are presented as n, unless otherwise stated. OCS: oral corticosteroids; sig.: significant; NS: nonsignificant. [#]: hazard ratio (95% CI).

TABLE 2 Summary of results from included studies by disease severity

First author, year [ref.]	Severe asthma (corticosteroid-dependent) A	Severe asthma (non-corticosteroid dependent) B	Mild to moderate asthma C	Non-asthmatics D	Side-effect	Comparison	OR (95% CI)	p-value
Bone and muscle complications								
Sweeney, 2016 [14]		808	3975	2412	Osteopenia	A+B versus C	5.26 (3.75–7.37)	<0.001
Barry, 2017 [21]						A+B versus D	6.68 (4.28–10.43)	<0.001
Barry, 2018 [20]					Osteoporosis	A+B versus C	5.23 (3.97–6.89)	<0.001
						A+B versus D	6.53 (4.63–9.21)	<0.001
					Fractures	A+B versus C	1.54 (1.06–2.22)	0.022
						A+B versus D	1.65 (1.14–2.39)	0.007
Sweeney, 2016 [14]	422	328			Osteopenia	A versus B	1.15 (0.73–1.81)	0.36
					Osteoporosis		1.21 (0.67–2.17)	0.44
					Fractures		3% versus 0.3%[#]	0.007
Adrenal complications								
Sweeney, 2016 [14]	422	328			Cushingoid symptoms	A versus B	6% versus 0.3%[#]	<0.001
					Adrenal insufficiency		3% versus 0.3%[#]	0.010
Cardiovascular system								
Sweeney, 2016 [14]		808	3975	2412	Hypertension	A+B versus C	1.35 (1.12–1.61)	0.001
Barry, 2017 [21]						A+B versus D	1.76 (1.44–2.14)	<0.001
Barry, 2018 [20]					Cardiovascular disease	A+B versus C	1.36 (1.02–1.81)	0.035
						A+B versus D	1.57 (1.14–2.15)	0.005
Sweeney, 2016 [14]	422	328			Hypertension	A versus B	1.59 (1.07–2.37)	0.012
					Cardiovascular disease		0.71 (0.39–1.30)	0.41
Metabolic complications								
Sweeney, 2016 [14]		808	3975	2412	Type II diabetes	A+B versus C	1.46 (1.11–1.91)	0.006
Barry, 2017 [21]						A+B versus D	1.76 (1.30–2.38)	<0.001
Barry, 2018 [20]					Obesity (BMI >30 $kg \cdot m^{-2}$)	A+B versus C	1.36 (1.16–1.59)	<0.001
						A+B versus D	2.04 (1.74–2.39)	<0.001
					Hypercholesterolaemia	A+B versus C	1.15 (0.92–1.44)	0.21
						A+B versus D	1.61 (1.25–2.08)	<0.001
Sweeney, 2016 [14]	422	328			NIDDM	A versus B	3.48 (1.94–6.26)	<0.001
					Obesity (BMI >30 $kg \cdot m^{-2}$)		1.47 (1.10–1.97)	0.016
					Weight gain		12% versus 1%[#]	<0.001
Eye diseases								
Sweeney, 2016 [14]		808	3975	2412	Glaucoma	A+B versus C	1.12 (0.75–1.68)	0.58
Barry, 2017 [21]						A+B versus D	1.41 (0.89–2.25)	0.15
Barry, 2018 [20]					Cataracts	A+B versus C	1.89 (1.39–2.56)	<0.001
						A+B versus D	2.42 (1.70–3.43)	<0.001
Sweeney, 2016 [14]	422	328			Glaucoma	A versus B	0.83 (0.28–2.50)	0.98
					Cataracts		6% versus 0%[#]	0.002

Continued

TABLE 2 Continued

First author, year [ref.]	Severe asthma (corticosteroid-dependent) A	Severe asthma (non-corticosteroid dependent) B	Mild to moderate asthma C	Non-asthmatics D	Side-effect	Comparison	OR (95% CI)	p-value
Psychiatric disorders								
Sweeney, 2016 [14]		808	3975	2412	Psychiatric conditions/anxiety/depression	A+B *versus* C	1.43 (1.22–1.69)	<0.001
Barry, 2017 [21]						A+B *versus* D	1.67 (1.42–1.97)	<0.001
Barry, 2018 [20]					Sleep disorders	A+B *versus* C	1.70 (1.13–2.53)	0.010
						A+B *versus* D	2.21 (1.46–3.35)	<0.001
Sweeney, 2016 [14]	422	328			Depression/anxiety/low mood	A *versus* B	2.57 (1.76–3.76)	<0.001
					Sleep disturbance		4% *versus* 1%[#]	0.003
Gastrointestinal complications								
Sweeney, 2016 [14]		808	3975	2412	Dyspeptic disorders	A+B *versus* C	3.99 (3.37–4.72)	<0.001
Barry, 2017 [21]						A+B *versus* D	4.88 (4.11–5.79)	<0.001
Barry, 2018 [20]								
Sweeney, 2016 [14]	422	328			Dyspeptic disorders	A *versus* B	1.96 (1.45–2.64)	<0.001
Various								
Sweeney, 2016 [14]	422	328			Skin conditions	A *versus* B	4% *versus* 0.3%[#]	0.002
					Obstructive sleep apnoea		2.80 (1.48–5.29)	<0.001

Data are presented as n, unless otherwise stated. BMI: body mass index; NIDDM: non-insulin dependent diabetes mellitus. [#]: the publication did not provide odds ratios for side-effect with few events; in this review we provide percentages in these cases instead if a threshold of >1% was reached in any group.
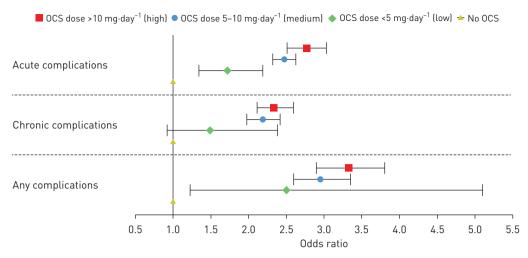
FIGURE 1 Risk of developing oral corticosteroid (OCS)-related complications by OCS dose exposures. OCS doses <5 mg·day^{-1} are considered low, 5–10 mg·day^{-1} medium and >10 mg·day^{-1} high. OR >1 describes a higher risk for developing OCS-related side-effects. Reproduced and modified from [23] with permission.

medium- (5–10 mg·day^{-1}) and high-dose (>10 mg·day^{-1}) OCS treatment, respectively [23]. In a British study, the estimated direct healthcare 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 et al. [24] study showed similar results, with a significant dose–response relationship found for side-effects in patients with severe asthma who received OCS. 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^{-1} than in patients receiving <6 mg·day^{-1}. Patients receiving >12 mg·day^{-1} showed the same pattern as those receiving 6–12 mg·day^{-1}, but in most cases with a numerically higher risk of OCS-related complications.

The study by CURTIS et al. [29] surveyed the use of OCS by patients, of whom 12% had asthma, and patient-reported adverse events. The study showed that the proportion of patients reporting side-effects of OCS as "bothersome" or "very bothersome" increased with increasing cumulative dose. Regular treatment with 5 mg prednisolone-equivalent per day for 1 year already resulted in an increase in adverse events of ~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 were 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 eight commonly attributed self-reported corticosteroid-associated adverse events 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 multifaceted. 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. Conversely, 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 no significant impact on QoL despite the dose reduction of OCS [36]. In the British Thoracic Society (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 [11] 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) lead to complications, as described in 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-term 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 Optimum Patient Care Research Database (OPCRD) dataset. The health economic impact of severe asthma, showing mean annual total costs of GBP 560–1324 for non-asthmatic patients compared to GBP 978–2072 for mild/moderate asthma and GBP 2603–4533 for severe asthma [21]. LEFEBVRE *et al.* [22] calculated that the costs for patients with low-, medium- and high-dose intensity were USD 678, USD 1181 and USD 2140 higher, respectively, than those of OCS non-users due to OCS-related complications. Another important conclusion of our literature review is that clinicians ought to pay high attention to prevention of OCS side-effects (*e.g.* substitution with calcium, vitamin D, recommend physical exercise, *etc.*), as they occur more consistently and widely and are more costly than previously thought.

This review is limited to adult patients, and can therefore not be generalised to paediatric populations. Additionally, 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 included in the review, a total of seven datasets and nine publications were finally consulted to summarise the effects of OCS treatment-related side-effects in asthmatic patients.

The study by DALAL *et al.* [23] based on US claims data from two Truven Health MarketScan Research databases provided data on the side-effects of OCS in a large cohort of patients with severe asthma, 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.* [22, 24], who based their research on Medicaid claims data in the US, but also used a longitudinal observational cohort study design. ZAZZALI *et al.* [26] used US commercial healthcare claims in a matched cohort study and ZEIGER *et al.* [27] presented administrative pharmacy and healthcare utilisation data gathered from the Kaiser Permanente Southern California Research Data Warehouse in a retrospective observational cohort study. All the above data sources would have been missed by focussing on randomised 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, categorisation of providers and locations of service and selecting the most useful measures of utilisation and expenditures [38]. The study by DAUGHERTY *et al.* [25] was longitudinal in design, but did not use claims data. Instead, the study was based on the UK Clinical Practice Research Datalink database.

Unlike the longitudinal studies, the studies by SWEENEY *et al.* [14] and BARRY and co-workers [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 contribute to the above findings. The significantly higher prevalence of comorbidities such as diabetes and hypertension in asthmatics *versus* non-asthmatics reported by SU *et al.* [39] may explain the increased risk of chronic kidney disease found in patients with severe asthma by SWEENEY *et al.* [14], 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 $\geqslant$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 ($\leqslant$7.5 mg·day^{-1}) was already regarded as medium [22–24] or high exposure [25, 27].

A different approach was used by Zazzali et al. [26]: high OCS use was defined as more than >30 days of OCS supply per year resulting in a median daily dose of ∼3.5 mg·day^{-1} in the included patients. This is comparable with the low-dose groups defined by Dalal et al. [23] and Lefebvre et al. [22, 24].

Patients with severe asthma in the BTS registry took on average 15 mg·day^{-1} OCS [14]. Obviously, most patients with severe asthma in the BTS registry therefore received much more than the recommended GINA dose of $\leqslant$7.5 mg·day^{-1} [14]. Most patients in the comparator group probably received the equivalent of an average daily dose of 1–5 mg·day^{-1}. 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. [23], Daugherty et al. [25], Lefebvre et al. [22, 24] and Zazzali et al. [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 presents as a continuum, starting even at very low doses <5 mg·day^{-1}. 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 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, it 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 such as omalizumab, benralizumab, reslizumab and mepolizumab as a preferred treatment choice over the use of OCS. German guidelines already recommend initiating 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]. Patients with severe asthma may benefit from disease phenotyping in terms of disease control and treatment-related adverse events [7].

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