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The patient's perspective of the adverse effects of glucocorticoid use: A systematic review of quantitative and qualitative studies. From an OMERACT working group

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ABSTRACT

Introduction. Glucocorticoids (GCs) remain widely used. However, the impact of GCs from the perspective of the patient, rather than of the clinician, remains relatively unexplored. Additionally, no general patient reported outcome measure has been developed to assess the effects of GCs across rheumatological conditions. The aim of this literature review was to identify the adverse effects of systemic GC use that are of importance to patients.

Methods. OVID EMBASE, OVID MEDLINE, PsycINFO and CINAHL was searched relating to three concepts: GCs, the patient perspective and adverse effects. A meta-synthesis of the qualitative data was performed separately by two independent researchers before qualitative metasummary was utilized to quantitatively aggregate the findings (combining quantitative and qualitative results), including the derivation of frequency and intensity effect sizes to identify those outcomes most prominently featured across all reviewed articles.

Results. The initial search retrieved 1,356 articles, of which 25 (18 quantitative, 7 qualitative) were deemed suitable for quality assessment and data extraction. Four major themes emerged amongst the 71 discrete outcomes: physical symptoms (44), psychological symptoms (18), effect on participation (6) and contextual factors (3).

Conclusions. Patients with a broad range of inflammatory diseases and demographic features describe key cross-cutting themes in relation to GCs and their impact on health-related quality of life. This work will inform the development of a core domain set for clinical trials involving GCs and a patient reported outcome to measure impact of GCs from the patient's perspective.

Introduction

Since their introduction as pharmacological agents in the 20th century, systemic glucocorticoids (GCs), such as prednisone, prednisolone and methylprednisolone have become and remain important therapeutic options in many diseases, most notably systemic inflammatory conditions. This is in part due to their rapid onset of action and favorable cost profile over other disease-modifying antirheumatic drugs (DMARDs) and other immunomodulatory agents [1]. However, both short-term and long-term GC use is associated with adverse effects (AEs) such as weight gain, mood disturbances and hyperglycemia with the severity and frequency of these effects often related to dose and duration of therapy. Although most GC AEs have been well characterized, there remains a relative lack of knowledge regarding the absolute risks of these AEs, including which are of

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most importance to patients [2]. In addition, the positive aspects of GC use from the patient perspective are also not well understood.

With ongoing efforts in drug development, a number of steroid-sparing agents are now being evaluated or are already in use clinically [3,4]. In order to be able to rigorously compare these novel agents to GCs in regards to efficacy and particularly AEs and safety, accurate measurement of the frequency and intensity of GC effects (positive effects and AEs) from the patient's perspective is required [5,6]. Although, a number of disease-specific patient-reported outcomes have been described [7,8], a prior literature review by this group (under the auspices of the OMERACT GC Impact Working Group) did not identify any patient reported outcome measure (PRO) that could be used to assess the effects of systemic GC use across the multitude of inflammatory conditions for which GCs are used [9,10].

In order to develop a data-driven PRO that can be used across all systemic inflammatory diseases, a detailed understanding of the current literature is required as one of the underpinning steps in the development of a PRO for GCs that can be used across all systemic inflammatory conditions. Traditionally, literature reviews have included only quantitative studies, however, qualitative research is increasingly recognized for its importance, particularly in an era that prioritizes the patient perspective as a quality indicator. Additionally, newer methodologies have been developed to allow for a semi-quantitative analysis of qualitative research. Therefore, the aim of this study was to perform a systematic review of the literature, including both qualitative and quantitative studies, in order to identify the AEs of systemic GC use that are of importance to adult patients across any inflammatory condition.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement [11] and registered with the International Prospective Register of Systematic Reviews (PROSPERO), record number CRD42018081620 [12]. Covidence [13], an online systematic review platform was utilized to assist with study selection, data extraction and quality assessment.

Eligibility criteria

The inclusion criteria comprised: (1) adult patients (age >/= 18 years), (2) systemic glucocorticoid use (oral, intravenous or intramuscular) for any reason, (3) the evaluation of the patient's perspective of glucocorticoid use, (4) quantitative (survey) and/or qualitative research methodology and (4) published manuscripts. Case reports and conference abstracts were excluded from the review.

Information sources

OVID EMBASE, OVID MEDLINE, PsycINFO and CINAHL were searched from inception to October 2017 with no language filter applied. In addition, the reference lists of the selected publications were manually reviewed for additional publications.

Search strategy

The search was conducted around the MeSH terms related to three concepts: glucocorticoids, the patient perspective and adverse effects. The complete search strategy utilized for OVID MEDLINE is available in Appendix 1.

Study selection

Titles and abstracts were manually reviewed by two independent reviewers (JC and CH). Abstracts considered eligible by one or both reviewers proceeded to full text review. Any differences in opinion regarding eligibility after independent full text review, were resolved through consensus.

Data collection

Four reviewers (RB, JC, CH and SG) independently performed the data extraction (two reviewers per study). General items extracted included author(s), year of publication, journal of publication and sponsorship sources. Specific data extracted included: study design, study setting (primary, secondary or tertiary care), aim/objective, sampling method, theoretical framework (if qualitative), data collection and analysis methods, inclusion/exclusion criteria, diseases studied, number of participants and their characteristics, type of GC, mode of administration, information regarding dosage and duration of GC use (if available) and main results.

Quality assessment

The same four reviewers (RB, JC, CH and SG) independently performed the quality assessment (two reviewers per study). For qualitative studies, quality was assessed using the criteria developed by Walsh and Downe [14] which included assessment of the following domains: scope and purpose, design, sampling strategy, analysis, interpretation, reflexivity, ethical dimensions and relevance and transferability. Subsequently, a summary score ranging from A (high quality, low risk of bias) to D (low quality, high risk of bias) was then assigned to each study as previously described by Downe, Simpson and Trafford [15]. For quantitative surveys, quality was assessed using the criteria developed by Möhler and Meyer [16] which included assessment of the following domains: scope and purpose, research methods, ethics, design of the research tools, sample and sampling, data collection and data analysis. Each assessed item was assigned a score of yes (definitely present), no (definitely not present) or unclear. Those studies with a majority of 'yes' scores (>50%) were deemed overall to have a low risk of bias, those with a prevalence of 'unsure' scores were deemed overall to have a moderate risk of bias and those with a prevalence of 'no' scores (>50%) were deemed overall to have a high risk of bias.

Data analysis

After the initial data extraction, the findings from the qualitative studies were extracted and organized utilizing meta-synthesis independently by two reviewers (JC and JR). These were then grouped with the findings of the quantitative studies and qualitative metasummary was then utilized as an approach to produce a quantitatively orientated aggregation of the qualitative and quantitative findings [17].

In order to assess how commonly a specific finding was reported across studies, qualitative metasummary defined a method labelled as frequency effect size, calculated by taking the number of studies containing a specific finding and dividing this number by the total number of studies and expressing as a percentage. In order to avoid confusion with effect sizes as thought of in quantitative methodology, we have labelled this metasummary frequency effect size (MFES). Finally, in order to assess which studies contributed to the final set of abstracted findings, qualitative metasummary also defines a method labelled as intensity effect size. This is calculated, initially for all findings, regardless of frequency effect size (derived by dividing the number of findings contained in a single study by the total number of findings across all studies), in addition to findings with frequency effect sizes >25% (derived by dividing the number of findings with frequency effect sizes >25% in a single study by the number of findings with frequency effect sizes >25% across all studies) [17].

This will be termed metasummary intensity effect size (MIES), hereafter.

Results

Study selection

The database search yielded 1,356 references, which after the removal of duplicates identified 1,343 unique references. Following title and abstract review, 103 references were deemed potentially eligible and proceeded to full text review. After review of the reference lists, one further reference was retrieved for full text review [18]. Subsequently, 80 texts were deemed not to meet the inclusion criteria for the review for the following reasons: (1) conference abstract, (2) not survey or qualitative study design, (3) outcome not related to the effect of glucocorticoids, (4) outcomes unable to solely attribute to glucocorticoids, (5) incorrect route of administration, (6) glucocorticoids not part of the intervention, (7) incorrect patient population, 8) duplicate reporting of results therefore no new data reported. One additional qualitative study by a co-author (JR) published after the initial search strategy was also added to the final review [19]. Therefore, in total, 25 studies (18 survey and 7 qualitative) were included in the final review. The study selection process is summarized in Fig. 1.

Study characteristics

Information regarding the survey and qualitative studies included in the analysis are presented in Tables 1 and 2, respectively. Although the effects of GCs was not the primary focus of all the reviewed studies, the specific data regarding the effects of GCs was utilized in the qualitative metasummary. The quantitative studies ranged from single center to national surveys, with the number of participants ranging from 30-2,167. The qualitative studies had far fewer participants (10-50), as would be expected for this method of research. The included studies were predominantly carried out in the United States of America (9 studies) [8,19–26] and the United Kingdom (8 studies) [18,19,27–32], however, other countries were also represented including France [33,34], Canada [19,35], New Zealand [36], Australia [22], the Netherlands [7], Germany [37] and Morocco [38]. Although the majority of the studies looked at patients with inflammatory rheumatic conditions, non-rheumatic inflammatory conditions were also represented, including immune thrombocytopenic purpura [21,24,26,28,30,37].

Quality assessment

Of the 18 quantitative surveys, 11 were deemed to represent low risk of bias, 6 were deemed to represent moderate risk of bias and one to represent high risk of bias (Table 1). Summary quality scores for the seven qualitative studies are presented in Table 2. Of the seven studies, four were graded A (the study's credibility, transferability and confirmability were high), two were graded B (some flaws, unlikely to affect the credibility, transferability, dependability and/or the confirmability of the study) and one graded C (some flaws which may affect the credibility, transferability, dependability and/or the confirmability of the study).

Metasummary frequency effect sizes

Overall, analysis of all publications yielded 71 discrete outcomes of which four main themes emerged that are of importance to patients with regards to the effects of glucocorticoids, namely physical symptoms, psychological symptoms, effect on participation and contextual factors. These findings and their metasummary frequency effect sizes are presented in Table 3. Of these, those related to physical and psychological symptoms were most prominent with the highest frequency effect sizes including weight gain (74%), problems with sleep (74%), irritability and mood swings (74%), skin changes (65%) and upper gastrointestinal effects (65%). Of note, outcomes related to participation and contextual factors were derived predominantly from the qualitative studies alone.

Metasummary intensity effect sizes

Calculated metasummary intensity effect sizes are presented in Table 4. The publication that presented the highest number of outcomes relative to the total number of outcomes was Van der Goes et al. [6] with a MIES of 38%, followed by the studies of Asl Baakhtari

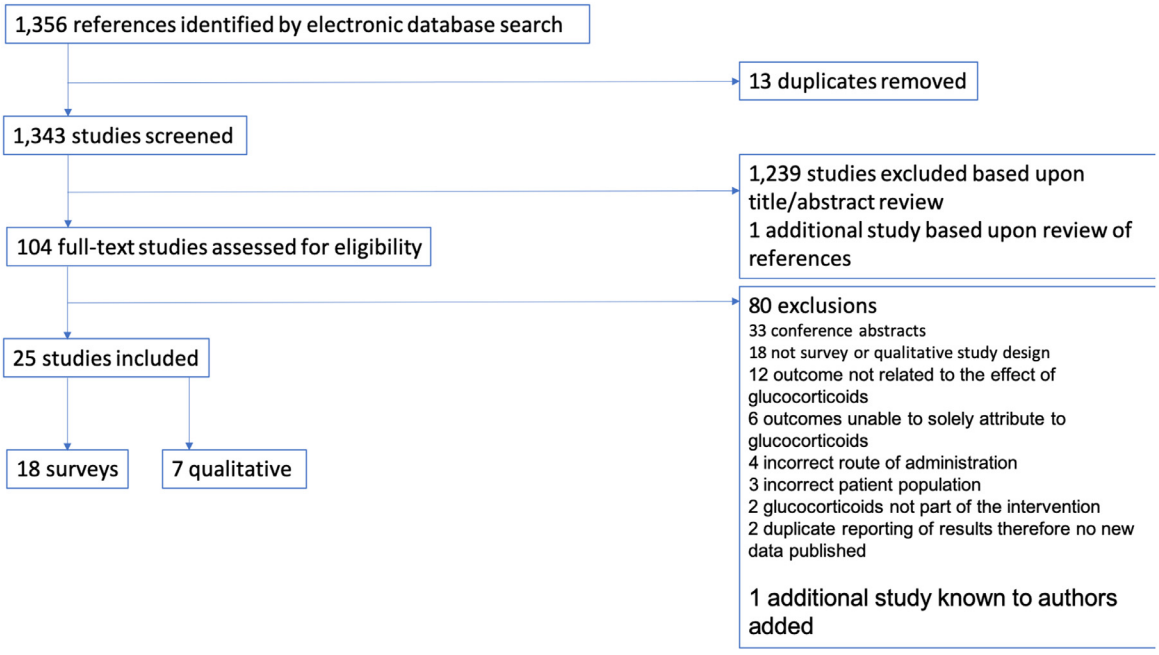

Fig. 1. Study selection process.

Table 1
Study characteristics of included quantitative (survey) studies.

Study	Country and participants	Diagnosis	Intervention	Objective	Outcome	Risk of Bias
Armstrong et al. 2015 [20]	United States of America N = 71	Primary or metastatic brain tumor	Questionnaire completed in person (Dexamethasone Symptom Questionnaire-Chronic)	To evaluate the signs and symptoms of prolonged corticosteroid use in brain tumor patients and to evaluate the utility of the Dexamethasone Symptom Questionnaire-Chronic	The three most frequently reported symptoms were trouble with sleep, increased appetite and anger, whilst the three most bothersome symptoms were appetite change/weight gain, anxiety/irritability and changes in sleep pattern. In addition, total cumulative steroid dose was associated with increased appetite, hiccups, roundness of face, depression and difficulty standing from a seated position.	Moderate
Asl Baakhtari et al. 2018 [36]	New Zealand N = 453	Inflammatory bowel disease	Online questionnaire	To understand patients' perspectives of glucocorticoid treatment	Efficacy, lack of previous adverse effects and positive side effects (for example increased energy) were associated with a willingness to use corticosteroids again, whereas weight gain and hallucinations were associated with an unwillingness to use corticosteroids again.	Low
Berti et al. 2008 [21]	United States of America N = 814	Immune thrombocytopenic purpura	Online questionnaire (modification of the Modified Transplant Symptom Occurrence and Symptom Distress Scale-Revised)	To describe the glucocorticoid-related symptoms experience in immune thrombocytopenic purpura and to compare experiences amongst patient who are current users, former users and never users.	Back pain, fatigue, sleep difficulties, muscle weakness and difficulty seeing well were reported to be the most frequently occurring and distressing symptoms. Current users and those who had stopped glucocorticoids less than six months prior reported more symptoms compared to those who had never received or stopped glucocorticoids greater than six months prior.	Low
Black et al. 2017 [22]	Australia and United States of America N = 150	Various rheumatic diseases	Questionnaire (mailed and online)	To determine the adverse effects related to glucocorticoids and explore which are of importance to patients	The majority of patients reported at least one adverse effect. Those identified as 'worse' in both cohorts included skin thinning/easy bruising, sleep disturbance, mood disturbance and change in facial shape. Additionally, most felt that glucocorticoids helped their disease 'a lot' and that benefits outweighed the adverse effects.	Low
Cooper et al. 2015 [27]	United Kingdom N = 233	Asthma	Questionnaire (online and mailed)	To examine the frequency of patient-reported side effects of glucocorticoids and to examine the impact bout concerns and side effect experiences on reported adherence	There was a high prevalence of reported side effects to glucocorticoids. Older age and male gender were associated with fewer side effects of oral glucocorticoids, however, concerns about glucocorticoids was associated with non-adherence.	Low
Costello et al. 2017 [28]	United Kingdom N = 604	Various rheumatic diseases Immune thrombocytopenic purpura Lung disease	Online questionnaire	To identify the side effects of most importance to glucocorticoid users	The side effects of most importance to patients were weight gain, insomnia and moon face	Low
Curtis et al. 2006 [23]	United States of America N = 2,167	Inflammatory bowel disease Obstructive airway disease heumatoid arthritis Systemic lupus erythematosus	Mailed questionnaire	To obtain prevalence estimates of glucocorticoid-associated side effects	More than 90% of respondents experienced at least one side effect with weight gain being most common. All adverse effects measured demonstrated a dose-dependent association with cumulative glucocorticoid dose.	Low

(*continued*)

Table 1 (*Continued*)

Study	Country and participants	Diagnosis	Intervention	Objective	Outcome	Risk of Bias
Fardet et al. 2007 [34]	France N = 80	Various rheumatic diseases Neutrophilic dermatitis	Questionnaire	To prospectively investigate the rate of and risk factors of clinical adverse events following the start of long term systemic glucocorticoids	Lipodystrophy was both most common and most distressing to patients. Other frequent adverse effects included neuropsychiatric disorders, skin disorders, muscle cramps and proximal muscle weakness.	Moderate
Fardet et al. 2009 [33]	France N = 115	Various rheumatologic diseases	Questionnaire	To understand patients' experiences of adverse effects of chronic glucocorticoids	Lipodystrophy, sin disorders, neuropsychiatric disorders and insomnia were reported by more than half of patients and were underestimated by physicians.	High
Forss et al. 2012 [46]	Worldwide N = 1245	Adrenal insufficiency	Online questionnaire	To investigate participants' self-perceived health status and outcomes by type of disease and therapy	The majority of participants were concerned about long-term side effects of steroid therapy including osteoporosis, obesity and cardiovascular morbidity.	Low
Guidry et al. 2009 [24]	United States of America N = 64	Immune thrombocytopenic purpura	Questionnaire (mailed or via telephone)	To understand the potential conflict regarding glucocorticoid side effects between Hematologists and patients	Responses of patients to the frequency of severe side effects to glucocorticoids was significantly different to those of Hematologists with patients reporting increased frequency for the majority of side effects.	Low
Guidry et al. 2009 [30]	United Kingdom N = 30	Immune thrombocytopenic purpura	Questionnaire	To validate previously gathered data regarding glucocorticoid side effects in a different patient group	Responses regarding severity of side effects did not significantly differ between the two patient groups.	Low
Jongen et al. 2016 [7]	Netherlands N = 85	Multiple sclerosis	Online questionnaire (Methylprednisolone Adverse Effects Questionnaire)	To assess the occurrence, severity and impact of adverse events during and after glucocorticoids	In the majority of patients, glucocorticoids led to the development of adverse effects, with impact upon activities of daily living.	Low
Matzdorff et al. 2007 [37]	Germany N = 80	Immune thrombocytopenic purpura	Mailed questionnaire	To evaluate what treatments are offered to German patients with chronic immune thrombocytopenic purpura	The majority of patients who had received glucocorticoids experienced side effects, most frequent being weight gain/increased appetite, moon face, depression/anxiety and restlessness/insomnia.	Moderate
Morrow et al. 2012 [35]	Canada N = 53	Multiple sclerosis	Questionnaire	To assess compliance to high dose oral glucocorticoids and identify barriers to compliance	Most patients experienced at least one side effect, most commonly insomnia, mood changes and increased appetite.	Moderate
Nassar et al. 2014 [38]	Morocco N = 125	Various rheumatologic diseases	Questionnaire completed in person	To identify glucocorticoid adverse effects of most importance to patients and physicians	The most common adverse effects reported included neuropsychiatric symptoms, weight gain and myopathy and the frequency compared to physician's perceptions were often different.	Moderate
Van der Goes et al. 2010 [6]	EuropeN = 140	Various rheumatologic diseases	Questionnaire	To explore the opinions of patients and rheumatologists towards glucocorticoid therapy	Osteoporosis, cardiovascular disease, diabetes and weight gain were ranked as most worrisome to patients and to a large extent corresponded to those voiced by rheumatologists.	Moderate
Walsh et al. 2001 [18]	United Kingdom N = 367	Fibrosing alveolitis Obstructive airway disease	Mailed questionnaire	To provide information on the prevalence of side effects in glucocorticoid users	The side effects of glucocorticoids were dose related and included fracture, cataracts, use of antacids, muscle weakness, back pain, bruising, oral candidiasis and having fewer teeth.	Low

Table 2
Study characteristics of included qualitative studies.

Study	Country and participants	Diagnosis	Intervention	Objective	Outcome (related to glucocorticoids)	Quality rating
Gamble et al. 2007 [29]	United Kingdom N = 10	Asthma	In-depth, non-structured one-on-one interviews	To describe participants' practices associated with glucocorticoid administration	Five main themes emerged: fear of side effects, knowledge is power, weighing up costs and benefits, loss of self and impact on lifestyle	A
Hall et al. 2007 [31]	United Kingdom N = 31	Inflammatory bowel disease	Mix of focus group discussions and individual interviews	To understand patients' beliefs about drug treatment and how this affected their use of medications	The main emerging themes centered on the acceptance and perceived necessity of the medications, the fears and concerns held towards medications and willingness to self-manage	A
Mathias et al. 2008 [26]	United States of America N = 23	Immune thrombocytopenic purpura	Focus group discussions	To develop a conceptual model to describe the impact of immune thrombocytopenic purpura and its treatment on patients' health-related quality of life	Adverse effects of glucocorticoids were most emphasized during the focus group discussions which influence multiple domains pertaining to health-related quality of life	B
Mathias et al. 2017 [8]	United States of America N = 33	Systemic lupus erythematosus	Semi-structured face-to-face interviews	To develop a patient reported measure to assess general impact, benefits, side effects and impacts associated with oral glucocorticoid use in systemic lupus erythematosus	Patients have mixed attitudes to glucocorticoids, reporting both positive and negative impacts of glucocorticoid therapy	B
Mathias et al. 2017 [25]	United States of America N = 14	Systemic lupus erythematosus	Semi-structured telephone interviews	To develop a comprehensive systemic lupus erythematosus-specific patient-reported outcome to assess patient satisfaction with treatment, treatment options and medical care	Although the majority of patients reported treatment efficacy with glucocorticoids, all reported adverse effects secondary to glucocorticoid therapy	C
Robson et al. 2018 [19]	Canada, United Kingdom and United States of America N = 50	ANCA-associated vasculitis	Semi-structured interviews	To describe the impact of glucocorticoid therapy on patients' health-related quality of life	Overarching themes included that glucocorticoids are effective at the time of diagnosis and during relapse, glucocorticoids are associated with emotional, physical and social effects and that there is a need to balance the risks and benefits of glucocorticoid therapy	A
Twohig et al. 2015 [32]	United Kingdom N = 22	Polymyalgia rheumatica	Semi-structured face-to-face interviews	To explore patient experiences of living with and receiving treatment for polymyalgia rheumatica	Initial glucocorticoid therapy was successful in treating symptoms in the majority of patients, however, the burden of side effects was also significant and for some were worse than the symptoms of polymyalgia rheumatic itself	A

et al. [36], Gamble et al. [29] and Nassar et al. [38] (all 34%). There were 19 outcomes with a MFES >25% (Table 3). Of all studies, those which presented the highest number of these high frequency outcomes were Asl Baakhtari et al. [36], Black et al. [22] and Berti et al. [21] (metasummary intensity effect sizes >25% of 95%, 84% and 79%, respectively).

Discussion

The aim of this systematic review was to identify the effects of glucocorticoid therapy that are of importance to patients and to summarize this data in a meaningful way in order to assist in identifying core outcomes to be utilized in future clinical trials involving GCs. The findings revealed that the effects of GCs, as recorded by patients, are numerous and fall into four main domains: physical symptoms, psychological symptoms, their effect on participation and contextual factors. The participation and contextual factors domains were captured in the qualitative studies and would have been missed if these studies had been excluded from the search strategy. The participation domain included important patient experiences such as the impact on sexual relationships and the impact on work. The contextual factors domain included the support, or lack of support of the community, friends and family. The most common outcomes of GC effects across all studies were weight gain and problems related to sleep, irritability and mood swings.

Since the initial literature search, an additional study related to this topic has been published. It used natural language processing to analyze narrative text in Twitter in relation to glucocorticoid adverse effects, identifying weight gain and insomnia as the most common adverse events [39], which is in keeping with the findings this review. One effect noted by Patel et al. and not captured in this review was that prednis(ol)one was described as not effective in a

Table 3
Themes, outcomes and their metasummary frequency effect sizes.

	Frequency effect size (%)
Physical symptoms	
Weight Gain (obesity)	74
Sleep (difficulty, trouble, insomnia, disturbance, restlessness)	74
Skin changes (acne, bruising, thin skin, atrophy, cutaneous complications, stretch marks, ichthyosis, brittle skin/fingernails, oily, fragile)	65
Upper GI problems (nausea/vomiting, stomach upset or acid reflux, peptic ulcer, dyspepsia, heart burn or gastric pain, bloating, indigestion, epigastric pain, irritation)	65
Cardiopulmonary (atherosclerosis, chest pain, dyspnea, palpitations, hypertension)	61
Change in Facial Features (bloated, swelling, moon, round, flushing, puffy)	57
Appetite (increase)	57
Muscle weakness (myopathy, pain, cramps, difficulty standing)	52
Increase blood sugar (diabetes, increased thirst)	52
Osteoporosis (thin bones, reduced bone strength, weakening of the bones)	48
Visual problems (eye disease, difficulty seeing well, glaucoma, cataracts)	43
Infection (recurrent infections, thrush, shingles)	35
Change in Appearance (not recognising oneself, lump in back, change in body shape, fat redistribution, lipodystrophy)	30
Edema (Swelling of feet or ankles)	30
Fatigue (asthenia, generalized weakness)	26
Fracture (loss of height since age 25, broken bones)	22
Musculoskeletal pain (back pain, arthralgia)	17
Impaired wound healing	17
Tremor	17
Amenorrhea/altered menstrual cycle	17
Oral complaints (sore mouth or throat, dental problems, sores on lips/mouth, loss of teeth, dryness of the mouth)	17
Hirsuitism	13
Osteonecrosis (hip)	13
Headache	13
Excessive sweating	13
Weight loss	9
Reduced appetite	9
Alopecia (hair loss)	9
Diarrhea or constipation	9
Improvement of symptoms (reduction in pain and stiffness, controlling flares, increased energy)	9
Taste of pills	9
Change in taste (metallic taste)	9
Dyslipidemia	9
Hot flushes	9
Withdrawal symptoms	5
Flare of symptoms of original disease on reduction	5
Effects due to interactions	4
Renal dysfunction	4
Cognitive disorder	4
Drowsiness	4
Dizziness	4
Dysphonia	4
Larger breasts	4
Hiccups	4
Psychological symptoms	
Irritability and Mood Swings (agitation, mood disturbances)	74
Depression or low mood (suicide attempt)	43
Anxiety	39
Hyperactivity/ euphoria (over optimistic feelings, manic, full of ideas)	30
Process of weighing up GC (cognitive load side effects vs benefits)	22
Anger	22
Personality change/ not feeling oneself (behavioral changes)	17
Relief at rapid resolution of symptoms	13
Fear of future effects (dependency, side effects, becoming immune)	13
Neuropsychiatric symptoms	9
Self-confidence (loss of identity, embarrassment)	9
Delaying seeking health care due to concern about starting GCs	9
Steroid induced psychosis	4
Additional tablet burden	4
Expectations about side effects did not match experience	4
Being perceived as different by friends or family	4
Hallucinations (strange/frightening thoughts)	4
Nightmares	4
Participation	
Impact on Sexual Relationships (loss of libido, reduced interest in sex)	13
Impact on Work	9
Impact on Family Role (mood)	4
Impact on Family Role (practical)	4
Impact on Friendships/social interactions	4
Treatment taking up time and thought	4
Contextual factors	
Support (lack of) Community or Media	13
Self-management and mastery	9
Support (lack of) Family and Friends	4

Table 4
Metasummary intensity effect sizes.

Publication	Intensity effect size (%)	Intensity effect size >25% (%)
Armstrong et al. 2015 [20]	20	53
Asl Baakhtari et al. 2018 [36]	34	95
Berti et al. 2008 [21]	32	79
Black et al. 2017 [22]	25	84
Cooper et al. 2015 [27]	7	16
Costello et al. 2017 [28]	15	58
Curtis et al. 2006 [23]	10	32
Fardet et al. 2007 [34]	25	63
Fardet et al. 2009 [33]	17	42
Forss et al. 2012 [46]	7	26
Gamble et al. 2007 [29]	34	53
Guidry et al. 2009 [24]	31	74
Guidry et al. 2009 [30]	8	32
Hall et al. 2007 [31]	14	16
Jongen et al. 2016 [7]	20	53
Mathias et al. 2008 [26]	14	37
Mathias et al. 2017 [8]	17	32
Mathias et al. 2017 [25]	10	26
Matzdorff et al. 2007 [37]	21	74
Morrow et al. 2012 [35]	15	42
Nassar et al. 2014 [38]	34	74
Robson et al. 2018 [19]	17	53
Twohig et al. 2015 [32]	14	26
Van der Goes et al. 2010 [6]	38	74
Walsh et al. 2001 [18]	13	32

number of Twitter messages. This may be due to the search strategy of the review, which aimed to identify studies looking at unintended GC effects, rather than efficacy.

A strength of this review was that it included studies reporting both quantitative survey responses as well as qualitative interviews. Traditionally, qualitative studies have not been included in systematic literature reviews due to challenges regarding the combination and summation of the data given the heterogeneous approaches to collection. Furthermore, there has been difficulty in combining the results of both qualitative and quantitative studies in a logical, presentable and useful manner. To overcome this, this study used qualitative metasummary, which allowed the synthesis and aggregation of these finding to be viewed as a whole. A limitation to this review is that most of the studies (and all of the qualitative studies) were conducted in high-income, developed countries, therefore potentially limiting generalizability of these results. Despite this, given the high metasummary frequency effect sizes across the studies which span a variety of medical conditions and patient populations, it is likely that

there is a core set of common effects which are experienced by glucocorticoid users as a whole. However, given that the dose and duration of GC use often varies between rheumatologic conditions, it is likely that an individual experience of GC use will be affected by these factors. This differing experience across diseases, doses and duration will be important to better understand as the role of GCs continues to evolve with the development of novel DMARDs and steroid-sparing agents.

An additional limitation is that given many of the results were presented as an aggregate combining the views of patients across a number of diseases, we were unable to assess how the patients' perspective varied by disease, an issue that the steps in PRO development would allow to be addressed. A further limitation is that in many of the quantitative studies, there was little or no description of the development and psychometric properties of the survey used and only two studies by the same group used the same survey [24,30]. Furthermore, only a minority [24,27,28,36] explicitly described patient involvement in the development of the survey. As a result, although the survey data was able to capture information regarding the experience of glucocorticoid use, due to their inherently structured and closed-ended nature, it is unknown if there were additional outcomes of importance that were missed in those populations. Furthermore, having a predetermined set of side effects of unclear derivation on a questionnaire is in itself biasing the patient perspective. Qualitative studies, by contrast, allow for a greater number and wider range of responses regarding a specific topic and so were specifically included to provide a broader and more complete view of the patients' perspective. In these studies, the effects that were grouped into the participation and contextual factors domains were much more prevalent. Therefore, despite the frequency effect sizes for these outcomes being lower and potentially seeming less important, this is due to them being represented in fewer studies overall. It is likely that they represent key areas of importance to patients that have historically not been well recognized by healthcare professionals. Although qualitative metasummary is a well-recognized method for synthesizing the results of qualitative and quantitative studies, this prior point highlights a limitation of the technique in that items which are assessed frequently across multiple studies, despite perhaps not being truly as important as an item which is less frequently assessed will be overrepresented in the final results.

At present, there are no published PROs for systemic glucocorticoid use in inflammatory disorders which cover the full range of effects demonstrated in this review. The Inhaled Corticosteroid Questionnaire [40] is a PRO developed for measuring the effects of inhaled GCs, but many of its items relate to local effects on the oropharynx, taste and voice and it has not been tested in patients on systemic glucocorticoids. In addition, the Systemic Lupus Erythematosus Steroid Questionnaire [8] was developed to measure the effect of systemic glucocorticoids but only in individuals with systemic lupus erythematosus (SLE). Although it includes outcomes related to impact on self-confidence and work, it has not yet been tested across a large population of patients and adequate psychometric properties have yet to be demonstrated in SLE or other conditions.

The recently developed Glucocorticoid Toxicity Index [41] is a comprehensive instrument designed to measure the effects of GCs across a number of conditions. It was designed to be used in clinical trials and is completed by an investigator at various study intervals to measure both the incidence and evolution of potential adverse effects. However, it is not a PRO and no patients were involved in the development of the instrument. Although the items capture many of the physical and psychological symptoms identified in this review, those related to participation and contextual factors are not represented. This, alongside previously demonstrated differences between the views of patients and healthcare professionals regarding important adverse effects of glucocorticoid therapy [6,38], underscores the ongoing need for the development of a data-driven PRO in this area. An instrument that captures the patient-perspective, particularly in regards to participation and contextual factors could be used alongside and complement the outcomes that are already contained within the Glucocorticoid Toxicity Index.

Finally, although this review has predominantly focused on the adverse effects of GCs, they would not have survived in clinical practice had they not had significant benefit across a number of inflammatory conditions. In rheumatoid arthritis specifically, the use of low doses of prednisone (5-10mg daily) in addition to standard non-GC therapy has been shown to improve measures of disease activity, both radiographic and patient-reported without significant increases in the frequency or severity of adverse effects [42,43]. Furthermore, results are awaited from the GLORIA trial of low-dose GC therapy in addition to standard of care for older individuals with rheumatoid arthritis, which has been designed to include a measurement of the development of adverse effects of GCs as a co-primary endpoint [44]. Similar data from other rheumatic diseases are awaited. As noted by Buttgereit and Bijlsma [45], there is likely a continuum of benefits and harms to GCs and the safe dose and duration of GC therapy will vary depending on an individual's diagnosis and co-morbidities, as well as their attitudes and expectations of treatment. Therefore, the development of a PRO that assess both the benefits and harms, of GC use will enable further exploration of the contexts in which the balance between these benefits and harms might vary.

This review will help to underpin the development of a PRO for people with rheumatic conditions who receive GC therapies. Effects of importance identified here will be helpful when developing an initial conceptual framework for the PRO, which will help to guide (but not dictate) the development of the PRO. As per FDA guidance on the development of PROs, in-depth qualitative interviews with patients with a range of rheumatic conditions, different demographics features taking a spectrum of GC treatments (in terms of dosage and duration), will be the key first stage to ensure the full spectrum of patient perceptions on GC are captured. Themes of importance will then be recast as candidate questionnaire items, which will undergo cognitive testing, linguistic analysis and then a large-scale survey to determine scale structure and measurement properties of the final PRO.

In conclusion, the patient-reported effects of GCs used for a variety of inflammatory indications, include physical and psychological symptoms, their effect on participation, and contextual factors affecting health-related quality of life. The inclusion of qualitative studies has broadened our understanding of GC adverse effects beyond the information quantitative studies can provide. In particular, they have highlighted that the patient perspective of adverse effects is directly impacted by the benefits of GC treatment, and that both sides of treatment effect need to be considered in the context of each other. In order to accurately identify and assess these effects, this work will inform the development of a core domain set for clinical trials involving GCs, work currently being carried out by the OMERACT GC Working Group, and subsequently a PRO to measure the impact of GCs from the patients' perspective.

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Appendix 1: example of search strategy used

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. exp Adrenal Cortex Hormones/ (386004)
2. corticosteroid*.mp. (95047)
3. glucocorticoid*.mp. (103578)
4. glucocorticosteroid*.mp. (3372)
5. steroid*.mp. (313541)
6. patient report*.mp. (24592)
7. patient perspective*.mp. (2972)
8. (patient* adj2 perspective*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9829)
9. patient perception*.mp. (3213)
10. (patient* adj2 perception*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (12052)
11. consumer perspective*.mp. (401)
12. (consumer* adj2 perspective*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (731)
13. consumer perception*.mp. (495)
14. (consumer* adj2 perception*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (874)
15. patient opinion*.mp. (360)
16. patient* opinion*.mp. (1364)
17. patient concern*.mp. (1639)
18. patient* concern*.mp. (3684)
19. (adverse adj2 effect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (184009)
20. (adverse adj2 event*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (145154)
21. (adverse adj2 outcome*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (41432)
22. (adverse adj2 reaction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (70579)
23. (side adj2 effect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (255981)
24. 1 or 2 or 3 or 4 or 5 (687762)
25. 19 or 20 or 21 or 22 or 23 (587456)
26. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (27483)
27. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (50774)
28. 24 and 25 and 27 (350)

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