Incidence and US Costs of Corticosteroid-Associated Adverse Events: A Systematic Literature Review

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ABSTRACT

Objective: The objective of this systematic literature review was to evaluate the incidences and risks for adverse events (AEs) associated with oral and parenteral corticosteroids. An assessment was performed to estimate the costs of such AEs.

Methods: A systematic review of literature published from 2007 to 2009 was conducted to identify the incidence rates and risk ratios of corticosteroid-related AEs. The review protocol was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The literature search was expanded to include additional search terms for psychiatric conditions, infections, and peptic ulcers. Costs obtained from a separate narrative literature review were applied to AEs likely to affect third-party payers in the United States.

Results: A total of 357 publications were identified from the primary (n = 323) and secondary (n = 34) searches. Of these, 310 were excluded because they did not evaluate AEs related to corticosteroids, were an excluded publication type, or for other reasons. A final list of 47 studies were used for data extraction. Across patient populations, the most frequently reported corticosteroid-associated AEs were psychiatric events, infections, gastric conditions, and fractures. Corticosteroid-associated AEs reported to occur at an incidence >30% were sleep disturbances, lipodystrophy, adrenal suppression, metabolic syndrome, weight gain, and hypertension. Vertebral fractures were reported at an incidence of 21% to 30%. Dose-response relationships were documented for fractures, acute myocardial infarction, hypertension, and peptic ulcer. The costs of managing AEs that may occur with corticosteroids can be substantial. The literature reported 1-year per-patient costs of up to $26,471.80 for nonfatal myocardial infarction, and per-event costs as high as $18,357.90 for fracture. The findings from the present review should be interpreted cautiously due to several limitations, including the retrospective design of most of the studies identified, risk for confounding due to underlying disease activity or patient population, and the relatively small number of studies that reported each AE association. As this cost analysis was preliminary, a comprehensive pharmacoeconomic analysis should be undertaken to confirm the findings.

Conclusion: Based on the findings from this review, systemic corticosteroids are a common cause of AEs that may be costly to payers. (*Clin Ther*. 2011;xx:xxx)

Key words: adverse events, corticosteroids, cost analysis, long-term treatment.

INTRODUCTION

Corticosteroids are important and commonly used medications because of their potent anti-inflammatory and immunosuppressive properties. Systemic corticosteroids are a mainstay of treatment for many conditions, including rheumatologic conditions (eg, rheumatoid arthritis, temporal arteritis, polymyalgia rheumatica, systemic lupus erythematosus [SLE]), allergic reactions, hepatitis, obstructive lung diseases (eg, asthma, chronic obstructive pulmonary disease), and inflammatory bowel diseases

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Table I. Relationship between clinical dosing and cellular actions of corticosteroids in rheumatic diseases.

Dosage*	Clinical Application	Genomic Actions (Receptor Saturation), %	Nongenomic Actions	
			Nonspecific	Cytosolic Glucocorticosteroid Receptor Mediated
Low (≤7.5 mg/d)	Maintenance therapy for many rheumatic diseases	<50	Not relevant	Unknown
Intermediate (>7.5–≤40 mg/d)	Initial treatment for primary chronic rheumatic diseases	>50–<100	Perhaps relevant but of minor importance	Perhaps relevant but of minor importance
High (>30–≤100 mg/d)	Initial treatment for subacute rheumatic diseases	Almost 100	Relevant	Relevant
Very high (>100 mg/d)	Initial treatment for acute and/or potentially life-threatening exacerbations of rheumatic diseases	Almost 100	Very relevant	Relevant or perhaps even very relevant
Pulse therapy (≥250 mg for 1–3 d)	For particularly severe and/or potentially life-threatening forms of rheumatic diseases	100	Most relevant	Relevant or perhaps even very or most relevant

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*Values are prednisone equivalent (mg/d).

(eg, ulcerative colitis, Crohn's disease).[1,2] Systemic corticosteroids are also widely used as a part of the immunosuppressive regimen after organ transplantation and in oncology as a part of chemotherapy.[2] In 2003–2004, corticosteroids were the 19th most commonly mentioned (ie, ordered, supplied, administered, or continued) class of drug at ambulatory care visits, used by an estimated 141.7 per 1000 persons in the United States.[3] Prednisone was the 15th most commonly mentioned drug in US ambulatory care visits, with 16.6 million mentions, or ~1% of all mentions of drugs.[3] Corticosteroids have dose-related anti-inflammatory and immunomodulatory effects that are mediated primarily by genomic mechanisms activated by corticosteroid binding to glucocorticoid receptors.[4] The direct relationship between corticosteroid dosage and degree of glucocorticoid receptor saturation is thought to explain the observation that clinical activity generally increases with increasing corticosteroid dosage (**Table I**).[4] Likewise, the nonspecific nongenomic activity of corticosteroids appears to play an increasing role in the therapeutic effect as dosage increases.[4]

Although corticosteroids are effective anti-inflammatory and immunomodulatory agents, they exact a toll with respect to adverse events (AEs) and toxicities. Corticosteroids have been associated with AEs that are common and may be severe or life-threatening. According to data from the Healthcare Cost and Utilization Project (HCUP),[1] corticosteroids were the most

common specific cause of drug-related AEs, accounting for 10.3% of all drug-related AEs and 141,000 hospital stays in the United States in 2004. The contribution of corticosteroids to morbidity is illustrated by findings in patients with SLE, who may be prescribed long-term corticosteroids. In the Hopkins Lupus Cohort Study (n = 539),[5] the cumulative dose of prednisone was associated with osteoporotic fractures (relative risk [RR] = 2.5), symptomatic coronary artery disease (CAD) (RR = 1.7), and cataracts (RR = 1.9). Each 2-month period of exposure to high-dose prednisone (defined as ≥60 mg/d for ≥2 months) was associated with a 1.2-fold increase in the risks for avascular necrosis and stroke. In a study based on a review of medical records from 11,359 clinic visits in 310 patients with SLE at the Montreal General Hospital, Montreal, Quebec, Canada, the past-year corticosteroid dose was found to be a predictor of the 2-year risk for CAD, and the 8 risk factors for CAD.[6]

Although the product costs of corticosteroids are relatively low, their total direct and indirect costs may be considerably higher than the price of the drugs themselves when the cost of managing short- and long-term AEs is considered. The cost of corticosteroid-associated AEs has been evaluated in few studies, each having limited representativeness or generalizability with respect to factors such as patient population and country (ie, variability in currency, costs of medical services, and treatment patterns).[7,8] Information on the costs of corticosteroid-associated AEs is important to physicians and payers in evaluating treatment strategies for conditions for which corticosteroids are prescribed. The present investigation evaluated the incidences of and risks for AEs associated with oral and parenteral corticosteroids in the general population, using a systematic review of interventional and observational studies published in the medical literature. A narrative review was used for determining the costs of the AEs likely to affect third-party payers in the United States.

METHODS

The present study was an extension and amplification of a review of the medical literature published from 1990 to 2007[7] of the costs attributable to corticosteroid-associated AEs based on population rates and costs in the United Kingdom, conducted by Manson et al.[7] Although that study reviewed costs in the United Kingdom, it was chosen as a foundation for this US-focused initiative because of its recency and its comprehensiveness relative to other assessments of corticosteroid-associated AEs.

The latter review identified 21 categories of oral corticosteroid-related AEs and reported, based on an analysis of selected AEs, that the cost of treating these events in the United Kingdom was at least £165 per patient per year (US $344 [2009 US dollars]). The present study extended the time frame for literature analysis to October 2009 and included searches on specific AEs.

Publications on corticosteroid-associated AEs were identified using a literature-search strategy developed to complement the methods of Manson et al.[7] A search protocol was developed a priori, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A brief summary of the search strategy is shown in **Table II**. Included were publications based on clinical trials, observational studies, reviews (for the purposes of identifying potential studies rather than for data extraction), or economic evaluations reporting AEs or tolerability profiles of systemic corticosteroids.

Non–English-language publications were excluded, as were publications on inhaled or intranasal topical corticosteroids, which may have lacked significant systemic absorption. Initially, publications appearing between April 2007 and October 2009 were eligible for inclusion; however, because some commonly reported AEs were not captured using those date limits, a secondary search was conducted to identify literature on psychiatric conditions, infections, and peptic ulcers. The second search was not limited to the 2007–2009 time period and was based on citations from other systematic reviews. Both searches were completed in March 2010.

One reviewer (E.S.) used the titles and abstracts identified in the initial literature search to identify potentially relevant publications, the full-text versions of which were retrieved. Study characteristics including design, patient characteristics, corticosteroid characteristics, and incidences and risk ratios of reported AEs were extracted and summarized on a standardized form for the included publications. To evaluate dose-response relationships, all corticosteroid dosages were converted to prednisolone-equivalent daily doses.

Using criteria previously used by Manson et al,[7,9] the quality of original research publications was evaluated with respect to patient selection, description/

Table II. Summary of the methods and strategies used for the literature search in this analysis of the incidence and US costs of corticosteroid-associated adverse events (AEs).

Method	Strategy
Databases	MEDLINE (via PubMed), April 1, 2007–October 31, 2009; EMBASE, April 2007–October 2009; Cochrane Library, April 2007–October 2009; abstracts presented at therapeutic conferences the past 2 years (2007–2009); citation lists of systematic and nonsystematic reviews, health technology assessments (2007–2009); internet sites of Agency for Healthcare Research and Quality, National Institute for Health and Clinical Excellence, and National Health Service Economic Evaluation Database
Search terms	MeSH terms: *glucocorticoids, pregnadienetriols, corticosteroid,* and *steroid (general)*; specific terms: *betamethasone, budesonide, cortisone, dexamathasone, fludrocortisones, hydrocortisone, methylprednisolone, prednisolone, prednisone,* and *triamcinolone*; general terms for AEs: *side effect, adverse event, adverse effect, safety,* and *tolerability*; specific terms for AEs: *osteoporosis, fracture, osteopenia, bone mineral density (BMD), hypocalcemia, endocrine, diabetes, hyperglycemia, obesity, weight gain, adrenal suppression, adrenocortical insufficiency, Cushingoid, growth retardation/suppression, cardiovascular, hypertension, myocardial infarction/heart attack, stroke, atherosclerosis, neuropsychiatric, psychosis, mania, anxiety, depression, insomnia, infection, immunosuppression, candidiasis/candidemia, wound healing, cataracts, glaucoma, ocular effects, non-Hodgkin's lymphoma, acne,* and *peptic ulcer*
Publication inclusion criteria	Publications that reported AEs or tolerability profiles of systemic corticosteroids; study types: clinical trials, observational studies, or reviews; economic evaluations of drugs, treatments, or therapy; interventions; systemic corticosteroids (ie, oral or parenteral route) (see search terms for list of specific agents)
Publication exclusion criteria	Non-English language, dissertations or editorials, case reports, publications reporting non–corticosteroid-specific AEs, interventions, inhaled or intranasal corticosteroids (beclomethasone, flunisolide, fluticasone, mometasone), inhaled corticosteroids, populations infants (<1 year)

specification of the interventions, specification and analysis of the study, patient disposition, and outcomes. Each of the 5 criteria was graded on a scale of 0 to 2 (0 = information not available or criteria not met; 1 = partially described or partially met criteria; and 2 = fully described or criteria fully met), and scores for the individual criteria were summed to arrive at a total quality score ranging from 0 to 10. Based on the total quality score, studies were deemed to be high quality (score, 9 or 10), good quality (7 or 8), fair to good quality (5 or 6), poor to fair quality (3 or 4), or poor quality (1 or 2).[9] Studies that were poor to fair (≤4) were excluded from the analysis. Meta-analyses and abstracts (n = 5 publications) were excluded from this quality evaluation.

Cost Analysis

A cost analysis was undertaken to determine the economic burden of corticosteroid-induced AEs. Clinically relevant AEs considered likely to affect third-party payers in the United States were identified from the literature review. Because of the paucity of literature on US-only costs, the cost assessment was not restricted to US costs. AEs that were not directly related to a clinical event (eg, reduced bone mineral density) were excluded, as were AEs that were deemed to require only over-the-counter treatment or to be self-limiting.

A separate narrative literature search was undertaken to identify the costs of events that were identified from the systematic literature review. Cost data from

that search provided estimates of an event that would be anticipated to occur regardless of causality. These cost estimates were applied to the RR of the event occurring with corticosteroid therapy to derive the cost attributable to corticosteroids. This basic modeling approach was undertaken because no studies were identified that evaluated the incidences and costs of AEs directly attributable to corticosteroids.

To examine the potential reduction in economic burden achievable by reducing corticosteroid daily dose, a cost analysis was conducted on the AEs with the most clear dose-response relationship identified in the review: myocardial infarction (2 studies)[46,54] and fracture (8 studies).[19,25,44–46,49,51,54] The cost analysis evaluated the costs of AEs occurring with high daily doses versus low daily doses of corticosteroids based on the published literature. One of the limitations of this cost-analysis approach was the potential to overestimate or underestimate the actual costs of AEs. The published literature contains "cost" estimates, which may have included billed charges, negotiated payments or reimbursed amounts, or actual costs to the provider or system. Studies that presented charged amounts as the cost of an event may have overestimated the true cost to the provider or system. When possible, the actual costs of care were determined. However, many pharmacoeconomic studies used paid amounts based on published professional fee schedules or publicly available payment schedules (eg, Medicare Prospective Payment Systems) to estimate costs.

RESULTS

Study Disposition and Characteristics

The Figure shows the disposition of publications identified for the analysis. The number of unique, potentially relevant publications identified and screened for retrieval was 323, of which 47 (27 from the primary search, 20 from the secondary search) were included in the data extraction.[10–56] More than half of the 47 studies described in the publications were retrospective analyses (30 case–control studies, 10 cross-sectional studies, and 8 cohort studies). Twenty-one of the studies were conducted in Europe; United States, 13; Asia, 7; and other, 6. Of the 42 studies evaluated for quality, 9 were of high quality, 26 were of good quality, and 3 were of fair to good quality. A total of 4 studies were excluded from the analysis of AEs because of poor quality.[13,18,26,36]

One study was conducted in patients with acute conditions (acute optic neuritis); 26 were conducted in patients with chronic conditions; and 16 were conducted in the general population. Rheumatoid arthritis was the most commonly studied condition (7 publications) followed by acute lymphoblastic leukemia, asthma, SLE, pulmonary diseases, and nonspecified rheumatic disease (2 publications each). Twenty-four studies evaluated oral corticosteroid use only; the remaining 19 studies included parenteral administration or parenteral and/or oral administration. In the 18 studies in adults, ~38% of patients were male, and the mean age was ~56 years. The number of studies involving pediatric patients only was 6. A summary of the studies included in the analysis of corticosteroid-related AEs is shown in Table III.

Corticosteroid-Associated Adverse Events

The mechanisms by which corticosteroids induce undesired effects are complex and varied. The immunosuppressive and anti-inflammatory properties of corticosteroids, which are the primary source of their therapeutic value, are also the cause of untoward AEs, including an increased risk for infections.[57] On a molecular level, many of the other AEs are related to their effects on the endocrine system, electrolyte balance, and metabolism. Corticosteroids cause adrenal suppression through negative feedback of the hypothalamus, anterior pituitary, and adrenal gland.[57] The resulting adrenal suppression results in many of the commonly known AEs, such as Cushing's syndrome, adrenal insufficiency, and growth inhibition. In addition, reduced concentrations of adrenal hormones may play a role in the development of osteoporosis and neuropsychiatric disorders. Corticosteroids also cause electrolyte and fluid imbalance, including increased sodium reabsorption in the kidneys, increased urinary excretion of potassium and calcium, and decreased calcium gut absorption.[58] The resulting sodium retention and hypokalemia may cause elevated blood pressure (hypertension) and edema; the decreased calcium stores in the body contribute to the development of bone loss and fracture risk.[57–59] Bone formation is also reduced due to the inhibitory effects of corticosteroids on osteoblast activity.[59] Corticosteroids simulate glucose production by activating enzymes of gluconeogenesis; the result is an increased risk for hyperglycemia, new-onset diabetes, and cataracts.[57,58] Their catabolic activity includes increased inhibition of glu-

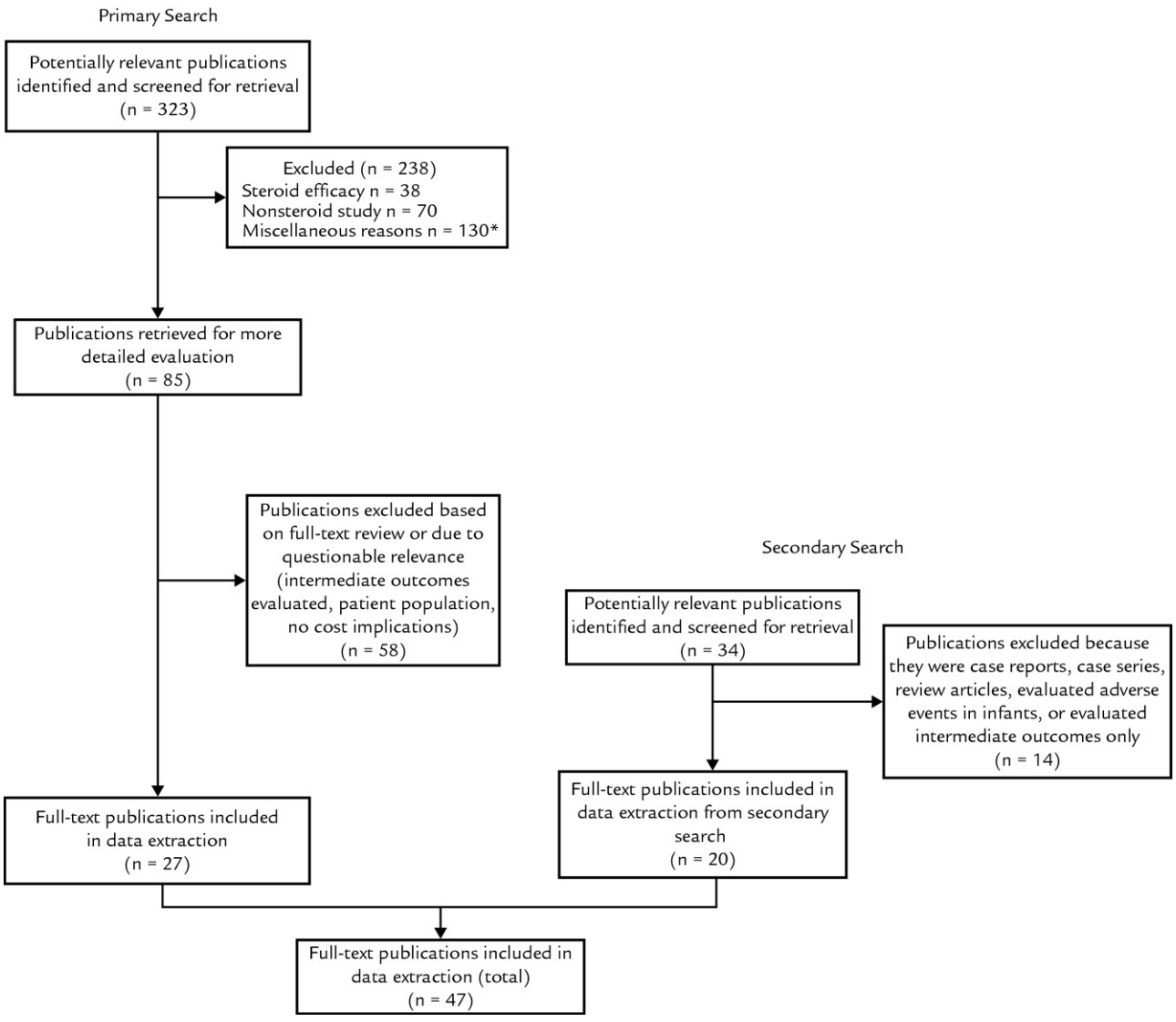

Figure. Disposition of publications identified in the literature search. *The main miscellaneous reasons included case study or series (n = 50), or that the study evaluated therapies to alleviate corticosteroid adverse events (AEs) without describing the incidence of AEs (n = 13). Other miscellaneous reasons included that the study evaluated the effects of corticosteroids in animal models or cell models or evaluated AEs in patient populations but did not specify corticosteroid use.

cose utilization in peripheral tissue and skeletal muscle protein breakdown (which can lead to muscle myopathy). Direct effects of corticosteroids that may result in AEs include increased gastric acid secretion (potential increased risk for ulcers), increased cardiac fibrosis (potential increased risk for myocardial infarction and other cardiovascular conditions), and neuronal changes (potential for psychiatric disorders).[57,58]

A wide variety of corticosteroid-associated AEs was reported across patient populations. In the 27 studies identified from the primary literature search, the most frequently reported AEs (assessed as the number of unique times a specific AE was reported in the publications) were psychiatric events (6 reports), fractures (4), and cancer (1 each of malignant melanoma, squamous cell carcinoma, basal cell carcinoma, and non-Hodg-

Table III. Summary of studies identifying adverse events (AEs) associated with corticosteroids based on data from the published literature in this analysis of the incidence and US costs of corticosteroid-associated AEs.

Study	Study Design	Quality Score*	Corticosteroid Studied	Reported AEs
Akerkar et al (1997)[10]	Cross-sectional study in 115 patients with Crohn's disease	7	Hydrocortisone	Hypertension, mental status change, hypokalemia, hyperglycemia, nosocomial infection, congestive heart failure
Avina-Zubieta et al (2009)[11]	Retrospective cohort study of data from 6981 patients with rheumatoid arthritis	n/a	Any	Myocardial infarction
Bolanos et al (2004)[12]	Prospective cohort study in 34 patients with asthma or rheumatic disease	8	PD 7.5 mg/d for 6 mo	Mania/hypomania, depression
Boston Collaborative Drug Surveillance Program (1972)[13]	Cross-sectional study in 676 hospitalized inpatients	4	PD	Psychosis/inappropriate euphoria, GI reactions, hyperglycemia/diabetes, infection
Brown et al (2002)[14]	Prospective cohort study in 32 patients with asthma	7	PD for ≥7 d	Mood disturbances
Christiansen et al (2009)[15]	Case–control study in 20,221 patients and controls	8	PD, MP, DEX, hydrocortisone	Hospitalization for atrial fibrillation or flutter
Chrousos et al (1993)[16]	Randomized controlled trial in 457 patients with acute optic neuritis	7	MP 1 g/d for 3 d + PD 1 mg/kg for 11 d or PD 1 mg/kg for 14 d then tapered	Sleep disturbance, mood disturbances, stomach upset
Conn and Poynard (1994)[17]	Meta-analysis of data from 6602 patients	n/a	Any	Peptic ulcers (new or exacerbated), bacterial sepsis, tuberculosis, diabetes, osteoporosis, hypertension, psychosis
Da Silva and Schiff (2007)[18]	Cross-sectional study in 5 patients receiving neuro-oncologic care	2	Any	Secondary adrenal insufficiency
de Vries et al (2007)[19]	Retrospective cohort study of data from 191,752 patients	9	Any	Fractures (any, hip/femur fracture, vertebral fracture)
Dietrich et al (2009)[20]	Case–control study in 786 patients and controls	7	Any	Bladder cancer
Dowell and Bresee (1993)[21]	Case–control study in 35 patients and controls	6	Any	Varicella infection
Einaudi et al (2008)[22]	Randomized controlled trial in 64 patients with acute lymphoblastic leukemia	7	PD 60 mg/m^2/d or DEX 10 mg/m^2/d for 30 d	Severe adrenal suppression, severe infection and adrenal suppression
Fardet et al (2007)[23]	Prospective cohort study in 88 patients with chronic disorders	9	Any, ≥20 mg/d for ≥3 mo	Lipodystrophy
Fardet et al (2007)[24]	Prospective cohort study in 88 patients with chronic disorders	9	Any, ≥20 mg/d for ≥3 mo	Lipodystrophy, hypertension, hirsutism, spontaneous bruising, altered wound healing, swollen ankles, hand tremors, muscle cramps, proximal muscle weakness, insomnia, neuropsychiatric disorders, irritability, anxiety/depression, euphoria/hyperactivity, manic episode, epigastric pain, hyperphagia
Gabriel et al (1997)[25]	Cross-sectional study in 232 patients with rheumatic polymyalgia	7	Any	Diabetes, fractures (vertebral fracture, Colles' fracture, hip/femur fracture, femoral neck fracture), aseptic necrosis, cataracts, infection, GI bleed, hypertension, myopathy

(continued)

Table III (continued).

Study	Study Design	Quality Score*	Corticosteroid Studied	Reported AEs
Garcia-Berrocal et al (2008)[26]	Retrospective cohort study of data from 163 patients with sudden sensorineural hearing loss	4	MP 1 mg/kg/d tapered over 21–28 d	Cushingoid features, muscle weakness, hyperglycemia, reduction in libido, insomnia, vertigo, otorrhea, perforation of the tympanic membrane, peptic ulcer, osteonecrosis of femoral head
Greenberg et al (2007)[27]	Prospective cohort study in 11,429 patients with rheumatoid arthritis	n/a	PD	Infection
Hafstrom et al (2007)[28]	Subanalysis of randomized controlled trial in 67 patients with early-onset rheumatoid arthritis	10	PSL 7.5 mg/d for ≥2 y	Carotid atherosclerosis, endothelial function
Hernandez-Diaz and Rodriguez (2001)[29]	Nested case–control study in 2105 patients and controls	8	Any	Upper GI complications including gastric or duodenal damage, gastric or duodenal lesions, GI bleed, or perforated ulcer
Huscher et al (2009)[30]	Cross-sectional study in 1066 patients with rheumatoid arthritis	8	Any, >6 mo	Cushingoid phenotype, ecchymosis, leg edema, mycosis, parchmentlike skin, shortness of breath, sleep disturbance, cataracts, depression/listlessness, glaucoma, elevated BP, epistaxis, weight gain
Jensen et al (2009)[31]	Case–control study in 7821 patients and controls	9	Any	Non-Hodgkin's lymphoma, squamous cell carcinoma, basal cell carcinoma, malignant melanoma
Jick et al (2006)[32]	Case–control study in 497 patients and controls	9	Any	Tuberculosis
Kameda et al (2009)[33]	Prospective cohort study in 44 patients with rheumatic disease	7	Any, ≥0.5 mg/kg	Vertebral fracture, osteonecrosis of femoral head
Luo et al (2009)[34]	Prospective paired study in 67 patients in systemic lupus erythematosus	8	MP 1 g/d for 2 d, with 2-wk intervals	Gastric mucosal injury
Messer et al (1983)[35]	Meta-analysis of data from 3064 patients	n/a	Any, for ≥4 d	Ulcers, GI hemorrhage
Naber et al (1996)[36]	Prospective cohort study in 50 patients with ocular disease	4	MP, fluocortolone >150 mg/d for 8 d then tapered	Hypomanic syndrome, depressive syndrome
Nerome et al (2008)[37]	Cross-sectional study in 34 patients with rheumatic diseases	6	PSL, MP	Cataracts
Ng et al (2009)[38]	Retrospective cohort study of data from 45 patients with myeloma	5	DEX 40 mg for 4 d, then 4 d off for 28-d cycle	Adrenal suppression
Nishimura et al (2008)[39]	Prospective cohort study in 135 patients with systemic lupus erythematosus	7	PSL	Psychiatric disorders
Panoulas et al (2008)[40]	Cross-sectional study in 400 patients with rheumatoid arthritis	7	PSL >6 mo	Hypertension
Patel et al (1996)[41]	Case–control study in 167 patients and controls	7	PD, hydrocortisone	Varicella infection

(continued)

Table III (continued).

Study	Study Design	Quality Score*	Corticosteroid Studied	Reported AEs
Piper et al (1991)[42]	Nested case–control study in 1415 patients and controls	8	Any	Peptic ulcer
Te Poele et al (2007)[43]	Cross-sectional study in 1289 patients with acute lymphoblastic leukemia	7	DEX 6 mg/m^2/d for 14 d every 14 wk for 1 y	Death from infection
Proven et al (2003)[44]	Retrospective cohort study of data from 120 patients with giant cell arteritis	7	Any	Diabetes mellitus, fracture (hip/femur fracture, vertebral fracture, Colles' fracture, other fractures), GI bleeding, hypertension, infection, cataracts
Reyes et al (2007)[45]	Prospective cohort study in 55 patients	8	Any, for >6 mo	Vertebral fracture
Saag et al (1994)[46]	Retrospective cohort study of data from 112 patients with rheumatoid arthritis	8	Any, >1 y	Fracture, serious infection, GI bleed or ulcer, cataracts, diabetes, herpes zoster, myocardial infarction, stroke, glaucoma, death
Shibatani et al (2008)[47]	Cross-sectional study in 150 patients undergoing renal transplant	7	MP 500 mg or PSL 50 mg during surgery, then PSL 50 mg for 3–7 d for 6 wk, then 10 mg/d maintenance	Osteonecrosis of femoral head
Smyllie and Connolly (1968)[48]	Retrospective cohort study of data from 550 patients with respiratory disease	7	Any, for >1 mo	Diabetes, peptic ulcer, GI bleeding/hemorrhage, perforated ulcer, mental disturbance, collapsed vertebra, sudden death, obesity, hypertension
Sosa et al (2008)[49]	Cross-sectional study in 88 postmenopausal women	9	Any, ≥7.5 mg/d for ≥6 mo	Vertebral fracture
Stuck et al (1989)[50]	Meta-analysis of data from 2111 patients	n/a	Any	Infectious complications
Sugiyama et al (2009)[51]	Retrospective cohort study of data from 700 patients with collagen vascular diseases	7	Any, ≥20 mg/d for ≥6 mo	Vertebral fracture
Toms et al (2008)[52]	Cross-sectional study in 117 patients with rheumatoid arthritis	8	PSL	Metabolic syndrome
Uzu et al (2007)[53]	Prospective cohort study in 42 patients with primary renal disease	7	PSL, MP 30–40 mg/d for ≥4 wk	Diabetes
Varas-Lorenzo et al (2007)[54]	Nested case–control study in 4795 patients and controls	9	Any	Acute myocardial infarction

(continued)

Table III (continued).

Study	Study Design	Quality Score*	Corticosteroid Studied	Reported AEs
Vestergaard et al (2008)[55]	Case–control study in 137 patients and controls	8	Budesonide, PSL, hydrocortisone, MP	Fracture
Walsh et al (2001)[56]	Cross-sectional study in 367 patients with asthma, COPD, or fibrosing alveolitis	9	Any, for ≥6 mo	Fracture (vertebral fracture, hip/femur fracture, ribs/sternum fracture, wrist fracture, upper limb fracture, lower limb fracture, clavicle/scapula fracture), back pain, bruising, muscle weakness, height loss, cataracts, diabetes, hypertension, oral candidiasis, shingles

COPD = chronic obstructive lung disease; DEX = dexamethasone; GI = gastrointestinal; MP = methylprednisolone; PD = prednisone; PSL = prednisolone.

*Using criteria previously used by Manson et al,[7,9] the quality of original research publications was evaluated with respect to patient selection, description/specification of the interventions, specification and analysis of the study, patient disposition, and outcomes. Each of the 5 criteria was graded on a scale of 0 to 2 (0 = information not available or criteria not met; 1 = partially described or partially met criteria; and 2 = fully described or criteria fully met), and scores for the individual criteria were summed to arrive at a total quality score ranging from 0 to 10. Based on the total quality score, studies were deemed to be high quality (score, 9 or 10), good quality (7 or 8), fair to good quality (5 or 6), poor to fair quality (3 or 4), or poor quality (1 or 2).[9] Studies that were poor to fair (≤4) were excluded from the analysis. Meta-analyses and abstracts (n = 5 publications) were excluded from this quality evaluation.

kin's lymphoma in 1 study). In the 43 studies included, the most frequently reported AEs were psychiatric events (16 reports), infections (14), gastric conditions (12), and fracture/increased risk for fracture (11).* When only AEs that were reported to be significantly associated with corticosteroids were identified, gastric conditions were the most frequently reported AEs (11 unique reports), followed by infection (9 reports) and psychiatric events (8 reports) (**Table IV**). Corticosteroid-associated AEs reported in the literature to occur at an incidence of >30% were sleep disturbances, lipodystrophy, adrenal suppression, metabolic syndrome, weight gain, and hypertension. Vertebral fractures were reported at an incidence of 21% to 30%. Corticosteroid-associated AEs reported at an incidence <10% were severe gastrointestinal AEs (1%–5%), severe infections (0.2%–3.1%), and myocardial infarction (4%).

Table V shows the AEs categorized by risk measure (including hazard ratios [HRs], incidence risk ratios [IRRs], relative risks [RRs], and odds ratios [ORs]) across patient populations. The time frames over which risks were characterized varied among studies. Only AEs with a significant difference between patients who received corticosteroids and those who did not receive corticosteroids are listed. AEs having a strong association with corticosteroid therapy were fractures, cardiovascular disorders and events, gastrointestinal disorders and events, and infections.

Many AEs were associated with a dose-response pattern with increasing daily dose. A relationship between corticosteroid daily dose and the incidence of fractures was observed across several studies; when combined, the estimated risk ratio was ~1.0 at daily doses ≤7.5 mg and ~1.8 at daily doses of 7.5 to 15 mg.† In addition, a relationship between corticosteroid daily dose and the incidence of acute myocardial infarction was observed, with estimated risk ratios of 1.26 (95% CI, 1.02–1.57) at daily doses ≤10 mg and 2.15 (95% CI, 1.45–3.14) at daily doses >10 mg.[54] A relationship between corticosteroid daily dose and the incidence of peptic ulcer was observed, with estimated risk ratios of 2.1 (95% CI, 1.4–3.1) at daily doses ≤30 mg and 5.4 (95% CI, 1.9–15.5) at daily doses >30 mg.[29] Corticosteroids were associated with an increased risk for infection at doses ≥10 mg/d[27,30,50] and, specifically, with an increased risk for tuberculosis

*References 10–12, 14–25, 27–35, and 37–56.

†References 17, 19, 25, 33, 44–46, 49, 51, and 55.

Table IV. Adverse events (AEs) associated with corticosteroid use based on data from the published literature in this analysis of the incidence and US costs of corticosteroid-associated AEs.*

AE	No. of Studies That Reported Significant Association of ≥1 Event
Gastric condition	11
Infection	9
Psychiatric events†	8
Fracture	7
Bruising	4
Other‡	4
Cataracts	3
Diabetes/hyperglycemia	3
Hypertension	3
Muscle cramps/weakness	2
Myocardial infarction	2
Cancer	2
Lipodystrophy	2
Adrenal suppression	1
Cushingoid features	1
Edema	1
Osteonecrosis of femoral head	1
Weight gain	1

*Table provides a count of the number of unique times an AE was reported in the literature. For example, if 2 studies reported an increased incidence of ulcers associated with corticosteroid, ulcers were assigned a count of 2. The number of studies sums to more than 47 studies as each study may have reported >1 AE. Each AE was counted only once per study. For example, fracture was counted only once in a study that reported the prevalence of fracture in patients receiving <5 mg/d and in patients receiving 5 to 7.5 mg/d.

†Psychiatric AEs included anxiety, euphoria/hyperactivity, mental disturbance, depression, psychosis, mania/hypomania, and mood disorder.

‡Included height loss, hypokalemia, atrial fibrillation/flutter hospitalization, and parchment-like skin.

at a threshold dose ≥7.5 mg/d.[32] The risk for cataracts with corticosteroid use was found to be dose related.[30] Other corticosteroid-induced AEs appeared to have a dose-response relationship, but findings from the publications included in the review were inconsistent.

Cumulative corticosteroid exposure appeared to influence the risk for certain AEs. Two studies conducted using data from the Rochester Epidemiology Project database reported that a higher cumulative dose was a significant risk factor for any corticosteroid-related AE (Gabriel et al[25]: cumulative doses ≥1.8 g, $P = 0.0092$; Proven et al[44]: cumulative dose and P not reported). Consistent with the findings from the review by Manson et al, de Vries et al[19] found that the risk for fracture increased with cumulative exposure, especially in adults receiving high daily doses (≥15 mg). As the cumulative exposure increased from ≤1 to >5 g/d in patients receiving high daily doses, the risk for osteoporotic, hip/femur, and vertebral fractures increased substantially, although the 95% CIs were wide. For example, in patients who received ≥30 mg/d, the RR of hip/femur fracture was 3.13 (95% CI, 1.49–6.59), and the RR of vertebral fractures was 14.42 (95% CI, 8.29–25.08).

Two large meta-analyses included an assessment of cumulative exposure and the risk for peptic ulcers, with divergent results.[17,35] In a meta-analysis of randomized double-blind trials, Conn and Poynard[17] reported that the incidence of peptic ulcers appeared to increase with duration of treatment, although the OR for the risk for peptic ulcer was not statistically significant between the corticosteroid and control groups in those who received medication for <30 days, 1 to 3 months, 4 to 12 months, and >12 months (mean daily dose, 35 mg; mean cumulative dose, 2.2 g). In a separate analysis of controlled clinical trials, the risk for peptic ulcer was significantly higher in patients treated with corticosteroids for <30 days compared with the control group (5.0; 95% CI, 1.6–15.8). The risk was also significantly elevated in patients who received a cumulative dose of <1.0 g (3.5; 95% CI, 1.5–14.9).[35]

Other AEs reported to be associated with cumulative corticosteroid exposure included serious infections (small increased risk in 1 study: 1.25; 95% CI, 1.0–1.5)[46] and cataracts (mean cumulative exposure 11.7 g, 0.9 [95% CI, 0.36–2.3]; mean cumulative exposure 23.6 g, 2.5 [95% CI, 1.1–5.6]; and mean cumulative exposure 60.6 g, 3.1 [95% CI, 1.3–7.5]).[56]

Other Key Findings By Tissue/Body System

Adrenal Effects

Hypothalamic-pituitary-adrenal suppression and clinical sequelae (eg, thyroid dysfunction, sex hor-

Table V. Risk for corticosteroid-associated adverse events (AEs) based on data from the published literature in this analysis of the incidence and US costs of corticosteroid-associated AEs.*

AE	Risk Ratio 1–<2	Risk Ratio 2–<3	Risk Ratio 3–<5	Risk Ratio ≥5
Any fracture	X	X	X	–
Back pain	X	–	–	–
Bacterial sepsis	X	–	–	–
Basal cell carcinoma	X	–	–	–
Bladder cancer	X	X	–	–
Bleeding	X	–	–	–
Bruising	–	–	–	X
Cataracts	–	X	–	X
Cushingoid phenotype†	–	–	X	X
Diabetes	X		–	
Ecchymosis	–	–	–	X
Epistaxis	–	X	–	X
Gastric damage	–	X	–	–
Gastric lesions/ulcer‡	–	X	–	X
GI hemorrhage	X	–	–	–
Height loss of >2.5 cm	X	–	–	–
Hip/femur fracture§	X	X	X	X
Hospitalization for atrial fibrillation or flutter	X	–	X	X
Hypertension	X	X	–	–
Hypokalemia	X	–	–	–
Infection‖	X	X	–	–
Leg edema	X	X	–	–
Lethal infection‖	–	X	–	X
Mental status change	–	–	–	X
Muscle weakness	–	–	–	X
Myocardial infarction	X	X	–	–
Non-Hodgkin's lymphoma	–	X	–	
Nonlethal infections‖	X	X	–	
Oral candidiasis	–	–	–	X
Osteonecrosis of femoral head¶	–	–	X	X
Parchmentlike skin	–	X	X	–
Peptic ulcer‡	X	–	–	–
Ribs/sternum fracture	–	–	X	–
Sleep disturbance	X	X	–	–
Squamous cell carcinoma	–	–	–	X
Tuberculosis#	X	–	–	X
Ulcers	–	–	X	–
Upper GI complications	X	–	–	–
Upper limb fracture (not wrist)	–	X	–	–
Varicella infection	–	–	–	X
Vertebral fracture§	X	X	X	X
Weight gain	–	X	–	–

GI = gastrointestinal.

*Only AEs with a statistically significant difference in risk between patients receiving corticosteroids and those not receiving corticosteroids are listed. Some studies may have been underpowered to detect significant differences. The risk ratio could reflect a hazard ratio, an incidence risk ratio, a relative risk, or an odds ratio.

†Risk for Cushingoid phenotype increased with higher corticosteroid dose.

‡Risk for gastrointestinal ulcers/lesions varied by study and appeared to increase with higher corticosteroid dose.

§Risk for vertebral fracture and hip/femur fracture increased with higher corticosteroid dose and in certain patient populations (eg, the elderly).

‖Risk for infection varied by type of infection and by study.

¶Risk for osteonecrosis of the femoral head varied by study and patient population.

#Risk for tuberculosis varied by study.

mone reductions) were generally observed with high-dose corticosteroid therapy or therapy of long duration. At daily doses >60 mg, the incidence of adrenal suppression ranged from 34.6% to 87.5% across studies.[22,30,38]

Bone Effects

Fractures were among the most frequently reported AEs associated with corticosteroid use. The risk for fracture varied by anatomic site. In general, the risk ratio for any fracture in patients using systemic corticosteroids ranged from 1.60 to 1.75.[19,56] The risk for vertebral fracture with corticosteroid use was greater than that for fractures at other sites—approximately 3-fold higher than in patients who did not use corticosteroids.[19,56]

Cardiovascular Effects

Negative cardiovascular outcomes associated with corticosteroid therapy included acute myocardial infarction, atrial fibrillation/flutter, hypertension, and metabolic syndrome. Current users of corticosteroids had a ~2-fold greater risk for atrial fibrillation or flutter compared with hospitalized patients who had never received corticosteroids.[15] The risk for acute myocardial infarction was 40% to 60% higher in patients who received corticosteroids than in patients who did not receive corticosteroids (OR = 1.42[54] and 1.60[11]). The risk for cardiovascular AEs appeared to decrease after discontinuation of corticosteroids. In 2 studies, the risk ratio for acute myocardial infarction and atrial fibrillation/flutter decreased as the time since last corticosteroid use increased.[15,54] A relationship between corticosteroid daily dose and the incidence of acute myocardial infarction was observed, with an estimated risk ratio of 1.26 at daily doses ≤10 mg and 2.15 at daily doses >10 mg.[54] Corticosteroid-induced lipodystrophy, or redistribution of adipose tissue, was commonly observed with long-term corticosteroid therapy. In 2 prospective studies in the same group of 88 patients on long-term corticosteroid therapy at a daily dose ≥20 mg, the incidence of lipodystrophy exceeded 60%.[23,24]

Gastrointestinal Effects

Serious gastrointestinal events, including peptic ulcers, bleeding, and dyspepsia, were linked to the use of oral and parenteral corticosteroids in several studies.[25,29,35,42,44,46] However, reports regarding the risk for peptic ulcers and gastrointestinal bleeding and corticosteroid use were conflicting, with some studies reporting a strong association related to dose, and other studies failing to find an association. Some evidence suggests that the risk for gastric AEs associated with corticosteroid use was increased by factors including history of peptic ulcer disease, use of nonsteroidal anti-inflammatory drugs/aspirin, advanced age, and variances in specific gastric enzymes.[29,34,42,44]

Hematologic/Oncologic Effects

The review by Manson et al[7] reported a relationship between non-Hodgkin's lymphoma and corticosteroid use. In the 2 studies identified in the present analysis, increased risks for basal cell carcinoma and bladder cancer with corticosteroid use were documented.[20,31] A significant association between oral corticosteroid use and the risk for basal cell carcinoma was documented in a population-based case–control study from Denmark (IRR = 1.15).[31] The risk for basal cell carcinoma was increased slightly with duration of therapy, from 1.17 with a duration of >1 year to 1.22 with a duration of ≥5 years.[31] In a population-based case–control study conducted in the United States, a significant increase in the incidence of bladder cancer was found in patients who reported taking oral corticosteroids for ≤2 years (OR = 1.87).[20] The risk for bladder cancer was increased >2-fold for patients taking corticosteroids at the time of diagnosis (OR = 2.18), whereas a numeric but statistically nonsignificant increase in risk was found among former users.[20] Conclusions about these results should be made cautiously given the small sample sizes and the multifactorial etiology of cancer.

Infection

Corticosteroid use has been associated with tuberculosis, sepsis, pneumonia, bursitis, complicated urinary tract infection, herpes zoster, varicella-zoster, and fungal infections such as mycosis and oral candidiasis. The risk for infection with corticosteroids appears to be elevated with a daily dose ≥10 mg.[‡] However, the relative contributions of patients' exposure to oral corticosteroids versus the underlying condition being treated with corticosteroids to the increased risk for infections are unclear. The underlying conditions or concurrent use of immunosuppressive medications may have contributed to the risk for infection.

[‡]References 21, 22, 27, 30, 32, 41, 43, 46, and 50.

Metabolic Effects

Hyperglycemia and diabetes were frequently cited as AEs of corticosteroid use, with frequencies up to 4-fold greater than those in controls.[17,25,44,48] One study that evaluated the dose-response relationship reported that the incidence of weight gain was significantly increased with corticosteroid doses ≥5 mg/d (HR = 2.4; $P = 0.004$).[30]

Ocular Effects

The incidence of cataracts in corticosteroid users was high (range, 7%–34%).[25,30,37,44,46,56] The development of cataracts with corticosteroid use was observed at a low dose threshold (5 mg/d).

Psychiatric Effects

Mood changes, psychiatric disorders, and sleep disturbances were frequently reported with corticosteroid use, although the cause-effect relationship was often unclear.[12,14,24,30,39] The appearance of mania/hypomania was reported after long-term treatment with high-dose (dose ≥20 mg/d for ≥3 months) and low-dose (7.5 mg/d for ≥6 months) corticosteroids.[24] Depression was reported less often than mania or hypomania and was associated with long-term corticosteroid therapy at lower doses.[12–14]

Cost Analysis

The costs of managing the AEs associated with corticosteroid use as identified from the published literature are shown in **Table VI**. Two recent publications[7,8] evaluated the costs associated with corticosteroid-induced AEs; the remaining publications evaluated the costs of managing the AEs independent of association with corticosteroids.[60–69] Thus, the AEs were not necessarily attributed to corticosteroids in the studies identified. Costs per AE in the published literature were identified for bone, cardiovascular, metabolic, gastrointestinal, ocular, psychiatric, and hematologic/oncologic AEs, as well as for infections. The costs of fractures, stroke, and gastrointestinal complications were particularly high. The costs of managing specific AEs were substantial, with 1-year per-patient costs of up to $21,824.68 for peptic ulcer and $26,471.80 for nonfatal myocardial infarction and per-event costs of up to $18,357.90 for fracture.

Cost analyses to examine the potential reduction in the economic burden of AEs achievable by reducing the corticosteroid daily dose were conducted for myocardial infarction and fracture—the AEs with the clearest dose-response relationships identified in the literature review. Based on the risk for myocardial infarction in the general population and the risks and incidences of myocardial infarction associated with low and high daily doses of corticosteroids, reducing the daily dose of corticosteroids was estimated to avoid 19.4 myocardial infarctions per 10,000 persons, for a cost reduction of $513,553 (2009 US dollars) per 10,000 persons (at $26,472 for the first-year cost of managing a myocardial infarction[62] **Table VII**). Given the range of costs reported in the published literature, the same analysis was conducted using the cost estimate of $2942 per year reported by Manson et al.[7] If this cost were applied, the potential cost avoidance would be $57,072 per 10,000 persons. Based on the risk for fracture in the elderly population and the risks and incidence of fracture associated with low and high daily doses of corticosteroids, reducing the daily dose of corticosteroids was estimated to avoid 96 fractures per 10,000 persons, for a cost reduction of $1.76 million per 10,000 persons. Similarly, if the cost estimate of $14,064 per fracture from Manson et al[7] were used instead, the potential cost avoidance would be $1.35 million per 10,000 persons.

DISCUSSION

Corticosteroids are an integral aspect of management of many autoimmune and inflammatory conditions. Although corticosteroids have been reported to have substantial clinical benefit in many diseases, they have been associated with AEs, particularly with long-term treatment. The findings from this review support that systemic corticosteroids are a common cause of AEs. AEs reported with particularly high frequency (>30% of patients) with corticosteroids included sleep disturbances, lipodystrophy, adrenal suppression, metabolic syndrome, weight gain, and hypertension. AEs for which patients who took corticosteroids were at substantially greater risk (≥3-fold) compared with those in patients who did not take corticosteroids included bruising, epistaxis, infections, oral candidiasis, squamous cell carcinoma, muscle weakness, fractures, atrial fibrillation/flutter, Cushingoid phenotype, osteonecrosis of the femoral head, parchmentlike skin, tuberculosis, and gastrointestinal ulcers.

These data should be interpreted cautiously. Conducting systematic literature reviews on corticosteroid-related effects is challenging. Some studies did not addressed the potentially major impact of confounding

Table VI. Costs per adverse event (AE) based on data from the published literature in this analysis of the incidence and US costs of corticosteroid-associated AEs.

AE	Cost, $	Cost/Episode/Year (Inflated to 2009 US $)*
Skeletal		
Any fracture		
Pisu et al[8]	£6541.12 (cost per incident)	14,064.44
Schäcke et al[57]	8650.80	18,357.90
Vertebral fracture[9]	1500.00 (cost per incident)	1743.25
Hip fracture[9]	15,000.00 (cost per incident)	17432.5
Cardiovascular and metabolic		
Diabetes		
Pisu et al[8]	£2519.86 (cost/y)	5411.16
Hailey et al[9]	2900.00 (initial + 6-mo)	3370.29
Metabolic syndrome[58]	4476.00 (cost/y)	5201.87
Myocardial infarction		
Pisu et al[8]	£1369.95 (cost/y)	2941.84
American College of Rheumatology[59]	15,540 (first-year cost)	26,471.80
Stroke		
Pisu et al[8]	£7148.33 (cost/y)	15,350.36
Hailey et al[9]	21,000.00 (hospitalization + follow-up + rehabilitation)	24,405.55
Hypertension[9]	1300.00 (initial + 6-mo)	1510.82
Immunologic		
Gastroenteritis†[60]	6184.00 (per diem)	7818.21
Sepsis†[60]	7842.00 (per diem)	9914.36
Meningitis†[60]	10831.00 (per diem)	13,693.25
Tuberculosis, primary diagnosis†[60]	6118.00 (per diem)	7734.77
Pneumonia requiring hospitalization†[60]	4586.00 (per diem)	5797.92
Pneumonia, community-acquired[9]	1500.00 (per incident)	1743.25
Herpes zoster infection[61]	26,825.00 (per incident)	28,701.62
Varicella infection[62]	7993.00 (per incident)	10,512.17
Gastrointestinal		
Peptic ulcer[8]	£10163.28 (cost/y)	21,824.68
GI complication[9]	39,400.00 (surgery, hospitalization, outpatient care)	45,789.46
Ocular		
Cataracts		
Pisu et al[8]	£890.67 (cost/y)	1912.63
Hailey et al[9]	3800.00 (cataract surgery)†	4416.24
Hematologic/oncologic		
Non-Hodgkin's lymphoma[8]	£8210.21 (cost/y)	17,630.65
Psychiatric		
Sleep disturbance (insomnia)[63]	4755.00 (6-mo costs)	6011.58
Depression[64]	3296.00 (cost/y)	4747.01
Depression, non–treatment-resistant[65]	1455.00 (cost/y)	1913.57
Psychosis‡[66]	3416.00 (cost/y)	5622.67

*Inflated to 2009 dollars using the medical Consumer Price Index (www.bls.gov); costs in British pounds converted to US $.
†Medical charges. Charges may overestimate the actual cost to the provider or system.
‡Costs reflect patients with severe mental illness.

Table VII. Potential benefits associated with reducing the daily corticosteroid dose for myocardial infarction in the general population and fracture in elderly patients, based on data from the published literature in this analysis of the incidence and US costs of corticosteroid-associated adverse events.

Parameter	Risk in General Population, %	Increased Risk with High-Dose Corticosteroid		Increased Risk with Low-Dose Corticosteroid		Potential Benefits of Reducing Daily Dose
		HR (95% CI)	Incidence, %	HR (95% CI)	Incidence, %	
Myocardial infarction in general population	0.22	2.15 (1.45–3.14) (source: Varas-Lorenzo et al [2007][54]; dose >10 mg/d)	0.47 (25 more myocardial infarctions per 10,000 persons)	1.26 (1.02–1.57) (source: Varas-Lorenzo et al [2007][54]; dose ≤10 mg/d)	0.27 (5.6 more myocardial infarctions per 10,000 persons)	Avoidance of 19.4 myocardial infarctions per 10,000 persons; cost reduction of $513,553 per 10,000 persons
Any fracture in elderly patients	2.08	1.99 (1.82–2.16) (source: de Vries et al [2007][19]; dose 7.5–15 mg/d)	4.1 (414 more fractures per 10,000 persons)	1.53 (1.43–1.63) (source: de Vries et al [2007][19]; dose <7.5 mg/d)	3.2 (318 more fractures per 10,000 persons)	Avoidance of 96 fractures per 10,000 persons; cost reduction of $1.76 million per 10,000 persons

HR = hazard ratio.

by underlying disease activity. Furthermore, the increased risk reported for systemic corticosteroid use is not necessarily indicative of a high absolute incidence of all of these AEs. For example, osteonecrosis of the femoral head occurs with a low absolute incidence but occurs more commonly in patients who took corticosteroids than in those who did not. In addition, the types of AEs identified in the second literature search conducted for this review might have been affected by the search methodology, which involved searching for specific AEs (eg, psychiatric/neurologic, peptic ulcer, infection). The strategy of searching for specific AEs in the second literature search might have resulted in failure to detect other corticosteroid-associated AEs. However, the results were generally similar to those of similar previous efforts.[7,8] For example, in the study by Manson et al,[7] the most frequently reported corticosteroid-associated AE was fracture (28 studies), followed by gastric conditions (13 studies) and psychiatric conditions (11 studies). This pattern of results is similar to that in the present analysis.

Several other limitations were derived from the characteristics of the studies reviewed. Many of the studies analyzed in the present review were not prospectively designed to assess corticosteroid-associated AEs. Accordingly, methodologies for assessing and reporting AEs were inconsistent across studies. Most of the studies were retrospective and had small sample sizes. Most of the studies had other weaknesses that might have limited the generalizability of the results as evidenced by the quality assessment. Many of the studies identified in the review evaluated only a single AE or type of AE. Most of the studies included all corticosteroid users; therefore, it was not possible to evaluate trends by specific corticosteroid therapy or in specific patient populations. Because the evidence base for some of the AEs, such as hematologic/oncologic events, was relatively small, some general trends could not be discerned. Because of the generally poor quality of many of the studies and the heterogeneity in study designs and populations, any trends or patterns should be interpreted cautiously.

The incidence of many AEs (eg, fracture, acute myocardial infarction, weight gain, infections, psychiatric events) was directly related to daily corticosteroid dose. These dose-response relationships were manifest despite substantial variability across studies in study design, population, daily dose, conditions treated, and treatment duration. The dose-response pattern included threshold effects. Other corticosteroid-associated AEs also appeared to occur with an incidence directly related to daily dose; however, trends appeared

to be less robust. In many cases, the inability to discern a definitive trend was related to a small number of studies or reports, lack of information on risk ratios, conflicting study results, and heterogeneity of patient populations. In addition to dose, certain AEs appeared to have been associated with cumulative corticosteroid exposure. Fractures, serious infections, and cataracts were all reported to be significantly associated with cumulative dose. Conclusions regarding cumulative exposure were limited, however, as few studies directly reported on these associations. Attempts to determine cumulative doses to draw further conclusions were unsuccessful because most studies did not provide sufficient details to calculate the dose.

Little information on the cost of AEs directly associated with corticosteroids was identified in the published literature. Previous economic analyses reported that the incremental cost of corticosteroid-induced AEs was $344 per patient per year (inflated to 2009 US dollars),[7] or $540 per patient per 2-year period.[8] These costs took some, but not all, of the potential AEs into consideration, excluding psychiatric events, rare but costly events (eg, avascular necrosis of the femoral head), and other AEs identified in the literature search. The lack of information may be attributed in part to the difficulty in conducting cost research on AEs. Challenges of such research include those of identifying drug-attributable AEs with certainty, determining costs directly attributable to the AE (vs other operatives, eg, underlying disease), and the need to rely on retrospective analyses of data collected for reasons other than assessing AE costs. The limited information available does not allow for broad conclusions about the costs of corticosteroid-associated AEs. However, based on the findings from the literature, the costs of events that may occur with corticosteroids is high. For example, the 1-year per-patient cost of myocardial infarction was reported to be as high as $26,472; this cost would be incurred by the health care system regardless of the cause of the infarction. Similarly, the costs of peptic ulcer and fractures are significant at 1-year per-patient costs of up to $21,825 for peptic ulcer and up to $18,358 per fracture event. However, a comprehensive pharmacoeconomic analysis should be undertaken to confirm the findings of this preliminary cost analysis. Given the number of patients using long-term corticosteroids, the cumulative costs for a health plan could be substantial. Reducing the daily corticosteroid dose requirements may reduce the incidence of certain AEs, such as fracture and acute myocardial infarction, and thereby reduce the costs associated with corticosteroid therapy.

CONCLUSIONS

Based on findings from this literature review, systemic corticosteroids are a common cause of AEs that range from bothersome to patients to severe or life-threatening. Corticosteroid-induced AEs such as sleep disturbances, lipodystrophy, hypertension, and adrenal suppression were reported with high frequency; while the absolute incidence was low for other AEs (eg, acute myocardial infarction and infections), corticosteroids were still significantly associated with a greater risk of development. The risk of developing AEs increased with higher corticosteroid dose for fractures, hypertension, acute myocardial infarction, and peptic ulcer. The costs of these AEs may be substantial to payers and far greater than the product costs of the corticosteroid.

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