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REVIEW

The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use

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Summary
Oral corticosteroids (OCS) are a key part of therapy regimens for a diverse variety of conditions. Despite their efficacy, they are associated with a wide variety of adverse events. The purpose of this review was to identify the range of adverse events that have been reported to be related to oral corticosteroids, examine the factors that influence their incidence and estimate the economic burden caused by these adverse events. In 61 identified studies, 21 different categories of OCS related adverse events were reported with increased fracture risk being the category most frequently described. Most studies that examined factors linked to the incidence of OCS related adverse events found that dose, age, gender, duration of use, treatment history, smoking habits or cholesterol level were influential in determining risk. Additionally, a cumulative economic analysis of selected adverse events found the annual cost of treating these events in the UK to be at least £165 per patient taking OCS. The clinical and economic burden of OCS related adverse events highlights the need for OCS sparing therapies to be developed.

Contents

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Introduction

Since the first isolation of cortisol in 1950, corticosteroids have proved to be extremely effective in the treatment of acute inflammation and chronic inflammatory diseases. However, despite their clinical success, oral corticosteroids (OCS) are used sparingly due to a broad array of serious adverse events including bone fractures, osteoporosis, susceptibility to infections, hyperglycemia, and obesity amongst others. Although corticosteroids are typically prescribed for a wide range of patients with inflammatory conditions, it is most frequently prescribed for patients with respiratory conditions such as asthma or chronic obstructive pulmonary disease (COPD), who represent 40% of patients taking OCS in the UK, with skin diseases (6%), musculoskeletal conditions (6%) and neurological conditions (3%) being the next most common conditions being treated with OCS.[1] Despite the associated risks, data show that oral corticosteroids are used by as many as 0.9% of the adult UK population at any one time.[1] This figure increases with age, with 2.5% of individuals between the ages of 70 and 79 using corticosteroids. This has created a strong ongoing need for steroid-replacement therapy within pharmaceutical disease management.

Corticosteroids are thought to act by binding with cytosolic glucocorticoid receptors which causes a repression in the transcription of immunologically active genes. To a lesser extent, they also promote the transcription of anti-inflammatory genes, which are thought to be responsible for many of the adverse events associated with corticosteroids.[2]

There are many different ways of administering OCS therapy, all of which can influence the occurrence of adverse events. Firstly, there are several different drugs in the OCS family, with prednisolone and its pro-drug prednisone, being the most commonly prescribed.[1] Other OCS therapies are hydrocortisone, cortisone, methylprednisone, dexamethasone, triamcinolone, betamethasone, budesonide, fluocortolone and deflazacort. These often have niche applications in treating specific conditions. The duration of OCS treatment can vary significantly depending on the condition being treated and the patient response to treatment. For example, some asthma attacks can be efficiently managed with a short burst of OCS therapy[3] whereas some patients with Crohn's disease are dependent on long term OCS therapy in order to prevent disease exacerbation.[4] Different doses can also alter the risk of adverse events[5] and even when treatment with OCS is completed, risk for adverse events can linger,[6] making it difficult to assess the risk factors associated with OCS. Because most studies focus on either a single adverse event related to OCS treatment or adverse events in a specific population, there is a need for an overall understanding of the generalised risks conferred by OCS therapy across all patients.

While OCS adverse events can be severe and require resource-intensive treatment, the potentially large economic implications have not been examined. This is particularly relevant for measuring the economic value of steroid-sparing therapies in comparison to OCS therapy. Furthermore, since many studies only identify pre-selected adverse events which are not indicative of the broad spectrum of adverse advents known to be OCS-associated, it is not possible to use these studies to estimate the economic impact of OCS adverse events as a whole, hence the value of this review.

As the multi-faceted negative consequences of OCS therapy are becoming better understood, the drive to find OCS substitutes becomes more urgent. In some conditions, inhaled corticosteroids have replaced OCS and have been successful in reducing the incidence of adverse events due to less systemic exposure, but the same diverse profile of adverse events remains.[7] Steroid avoidance has become a key focus in the effective management of patients treated with OCS, leading to the development of many non-steroidal drugs that have comparable anti-inflammatory action.[8] However, in order to appreciate the value of these drugs, the wide picture of OCS adverse events must be considered in order to determine the real cost offsets achievable by these therapies.

Methods

Search strategy

A literature search of key databases including MEDLINE, EMBASE and Cochrane Library was performed to identify

studies that considered adverse events due corticosteroid treatment. Search terms included commonly used corticosteroids, i.e. prednisone, prednisolone, methylprednisilone, betamethasone and dexamethasone and adverse events common to corticosteroids such as myocardial infarction, hypertension, adrenal insufficiency and osteoporosis. The search covered the period January 1990—March 2007. A full illustration of the search can be found in Appendix I. All initial search hits identified were assessed for relevancy. Full papers were obtained for studies that appeared potentially relevant and were formally reviewed. Additional papers identified from the reference lists were also included.

Inclusion and exclusion criteria

Papers were considered relevant if they measured the prevalence of OCS adverse effects among oral steroid users, the relationship between the presence of OCS side effects and patient characteristics such as treatment history, age, gender, or duration of steroid use, the dose—response relationship, the threshold effect related to the dose of the corticosteroid or the presence of OCS side effects in cost-effectiveness models.

Papers were excluded if they only studied inhaled corticosteroids, or corticosteroids administered systemically/IV, were conducted in an infant population, did not examine adverse events due to OCS, examined adverse events that did not have direct clinical consequences (e.g. reduction in bone mineral density is a laboratory observation without direct consequences while osteoporosis or fracture are clinical events requiring specific treatment) or were not published in the English language. OCS studies that did not report adverse events or reported them as not being relevant were not included. Commentaries, letters, descriptive narratives and unpublished conference abstracts were also excluded.

Data extraction strategy

To guide the extraction of relevant data a standard data extraction form was developed. This form included: study objective; study design, population and setting; main outcome(s) measured; relevant results and adverse events reported; and study conclusions. Studies were entered in date order and categorised according to four primary study objectives: (1) the prevalence of OCS adverse effects among oral steroid users; (2) the relationship between the presence of OCS side effects and patient characteristics such as treatment history, age, gender, or duration of steroid use; (3) the dose—response relationship, or threshold effect related to the dose of the corticosteroid; and (4) the presence of OCS side effects in cost-effectiveness models.

If statistical significance was identified in a study, then only significant results were reported. The results were based on published data only, and authors were not contacted for clarification of trial reports.

Study quality evaluation

In order to assess the quality and strength of the papers, several criteria were graded on a scale of 0—2 on criteria put forward by Hailey and colleagues, as is detailed in Table 2. A score of 2 indicated full execution and detail of a specific criteria, 1 indicated partial consideration was given and 0 indicated that information was not available or the criteria was not met.

The total numerical score was then summed in order to assign the study a total quality grade of A—E, with A corresponding with a score of 9 or 10 out of 10 total points, B with 7 or 8 points, C with 5 or 6 points, D with 3 or 4 points and E with 1 or 2 points.[9] Studies rated A, B or C were considered to be of reasonable quality and studies rated D and E were considered to be substandard. The distribution of study quality can be seen in Fig. 1.

Cost analysis

An economic analysis was performed to estimate the additional economic burden caused by AEs directly related to OCS. For clinically discreet AEs-fracture, cataract, diabetes, peptic ulcer, stroke, myocardial infarction and non-Hodgkin's lymphoma- that had a reported relative risk (RR), the baseline incidence of these AEs was subtracted in order to identify the number of AEs that occurred as a direct result of OCS treatment (e.g. if the relative rate of an AE was 1.95 relative to controls, the rate of additional AE instances due to OCS treatment was $1.95-1.00 = 0.95$). This was then multiplied by the overall population incidence rate to determine the additional number of AEs caused uniquely by OCS in patients receiving treatment. Because the studies used to identify RR values were quality studies (A—C) with reasonable numbers of OCS patients (range 539—404,183), no correction factor was applied RR values. The cost per AE episode or cost per year of AE treatment was applied in order to calculate the economic burden per OCS treated individual for these particular AEs. This was done from a UK perspective using UK cost data wherever possible and using the incidence data of the UK population for all AEs. When more than one study reported the RR of an AE, the RR from the study with the largest patient population was used.

Results

A total of 246 abstracts were identified. Of these, a total of 117 articles were retrieved and upon review, 63 documents were included in this literature review. A summary of rationale for exclusion can be found in Table 1.

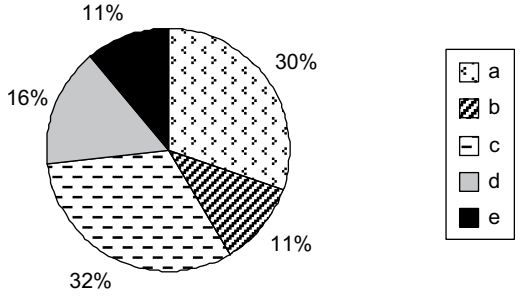

Figure 1 Study quality distribution.

Of the 63 documents included, 28 studies were retrospective reviews of medical records, 15 were prospective non-randomised trials, 10 were small randomised controlled trials (<50 patients per arm), 5 were large randomised controlled trials, 2 were meta-analyses, 1 was an economic analysis and 1 was a review paper.

All 63 studies reported adverse events related to therapy with OCS. A total of 1,221,575 unique patients on OCS treatment were included, with an average of 21,062 (range 8–404,183) patients per study, after accounting for studies that were conducted on the same patient population (but not accounting for unique analyses done using different patient selection criteria from the same database). A total of 14 studies (22%) had no placebo or control arms. These studies identified a wide range of OCS adverse events in a large variety of patient groups, confirming the broad spectrum of risk conferred by treatment with OCS.

Incidence of adverse events

Many studies included all patients treated with OCS regardless of primary diagnosis. The distribution of primary diagnosis of patient populations included in the studies is detailed in Table 3. Asthma patients were the most commonly studied group, followed by chronic obstructive pulmonary disease (COPD) patients.

Likewise, a wide variety of adverse events were attributed to OCS, with fractures being the most frequently cited followed by gastric conditions (Table 4). A complete synthesis of the occurrence of OCS related adverse events for all studies can be found in Table 5. All identified studies are included in this table regardless of OCS dose, treatment duration, patient population and presence of an appropriate control group. Due to the great heterogeneity of these studies, no attempt has been made to further synthesize these results in order to determine a representative mean increased risk.

Paediatric adverse events

Because a child's body is still developing and growing, OCS can cause a different profile of side effects compared to adults.[10] To examine this difference, studies that focused on children were isolated, and it was found that while several adverse events in children are common to the general adult population, impaired growth was uniquely reported in children and adolescents (Table 6). These differences were confirmed in a further study that compared the rate of OCS adverse events in vitiligo patients age 15 or younger ($n = 38$) and those older than 15 ($n = 43$).[11] Of the 13 different adverse events identified, facial swelling, weight gain and acne occurred significantly more frequently in adults than in youths and abdominal pain occurred more frequently in youths ($p < 0.05$ for all).

Table 1 Exclusion criteria.

Reason for exclusion	Total
Non-English paper	11
Did not meet eligibility criteria (i.e. age)	5
Specific adverse events not examined	55
Adverse events not clinically significant	23
Focus on non-oral corticosteroids	39
Focus on combined therapies	9
Focus on drug therapies to alleviate OCS side effects (i.e. bisphosphonates)	26
Focus of study not related to side effects due to use of oral corticosteroids	14
Total excluded	184

Table 2 Study performance classification criteria (Hailey et al., 2004).

Areas of interest	Points considered
Patient selection	Methods of randomisation/ selection; equivalence of intervention and control groups; drop-outs before start of intervention
Description/specification of the interventions	Adequate description for both intervention and control groups
Specification and analysis of study	Sample size; statistical methods used; clear specification of outcome measures
Patient disposal	Length of follow-up; drop-outs; compliance failures
Outcomes reported	Fullness and clarity of reporting; missing results; statistical summary; whether conclusions were consistent with data

Dose–response relationship

Several epidemiological studies have examined the dose–response relationship of oral corticosteroids, particularly in relation to fractures.[12–17,5,18,19,1] In these studies of all forms of OCS treatment, the highest doses (considered approx. >7–15 mg/day prednisolone equivalent) were universally found to be associated with the largest incidence of fractures, which were located in the hip, vertebrae or elsewhere in the body. Although the incidence of fractures generally increased with dose throughout the studies, there were a few isolated cases where the observed incidence of fractures was slightly lower in an intermediate dose compared to the low dose (i.e. Van Staa et al. 2000,[71] forearm fracture; Van Staa et al. 2005[20] osteoporitic fracture following low previous cumulative exposure). Additionally, de Vries and colleagues reported that patients with an intermediate dose had the highest risk of fractures. Apart from these anomalies, risk of fracture in adults with a higher dose increased between 41%[1] and 920%[5] compared to low dose OCS fracture incidence. This effect was also observed in children, who demonstrated a 20% increase in fracture risk at high dose, but only minimal differences were present between incidence of fracture at low and middle doses.[16]

Although dose–response relationship was most frequently reported in relation to fractures, several other adverse events were observed to have a dose–response relationship including diabetes/hyperglycemia,[21] cataracts,[5] ocular hypertension,[22] open-angle glaucoma,[22] bruising,[5] muscular

Table 3 Summary of patient populations studied.

Primary diagnosis	# Of studies (# of quality studies)[a]	Primary diagnosis	# Of studies (# of quality studies)[a]
Mixed[b]	22 (20)	Hormone-refractory prostate cancer	2 (0)
Asthma	8 (4)	Skin disease	1 (1)
COPD	6 (4)	Osteoporosis	1 (1)
Ocular condition	5 (3)	Cardiovascular disease	1 (1)
Arthritis	3 (3)	Polymyalgia rheumatica	1 (1)
Inflammatory bowel disease	3 (3)	Nephrotic syndrome	1 (1)
Lupus	3 (2)	Toxic ingestion	1 (1)
Childhood thrombocytopenic purpura	3 (1)	Alcoholic hepatitis	1 (1)
Skin disease allergic rhinitis	3 (0)	Vitiligo	1 (0)

[a] Quality studies are defined as those having an A, B or C grade on a scale of A–E.
[b] Studies enrolled all available patients taking OCS regardless of diagnosis.

weakness,[23] cardiovascular events[24–26] and cerebrovascular events.[26] Once more, the majority of studies demonstrated increasing incidence of adverse events with increased dose, with increases as high as 1034% in hyperglycemia for patients with very high OCS doses.[21] Taken together, the results overwhelmingly support the relationship between increased incidence of adverse events and high doses of OCS. Although the risk of adverse events is somewhat mitigated by lower doses, patients with low doses still exhibit a nearly universal enhanced risk for OCS related AEs.

Because the majority of these studies indiscriminately included all OCS users, it was not possible to assess whether the dose–response relationship varied according to specific OCS therapies.

Relationship between OCS adverse events and duration of use, treatment history, age and gender

There are many variables besides dose that can dictate the extent and severity of adverse events suffered by patients taking oral corticosteroids. The most commonly identified factor was duration of use, with seven studies examining the relationship between cumulative previous dose and adverse events.[24,27,20,26,14,16,22] In a patient survey of eight common AEs related to OCS (bone fractures, high blood sugar, cataracts, mood problems, weight gain, skin-bruising or thinning, acne and sleeping problems), all AEs were found to be more severe according to cumulative dose.[27] Van Staa and colleagues examined the risk of fracture and found that the risk of all types of fractures increase with higher cumulative dose ($\geq$1 g c. $<$1 g). Treatment with OCS for over 90 days, regardless of cumulative dose, also increased risk significantly ($p < 0.001$).[14] Garbe and colleagues found that increased cumulative OCS dose was related to an increase in ocular hypertension and acute angle glaucoma. Five different cumulative doses were examined, with a consistent increase of ocular AEs between the first four doses, although the highest cumulative dose exhibited a slight decrease in incidence. Another study[24] examined dose duration without considering cumulative dose and found that patients were 1.84 times as likely to experience a myocardial infarction with a short dose duration ($\leq$30 days) compared to a long dose duration ($>$31 days). Treatment history was also important in children who had increased risk following four or more courses of OCS.[16]

Other relationships were also reported, such as treatment history,[24,25,6,16] age,[20,17,18,28] gender,[20,6,18,28] treatment pattern,[14] smoking habits,[17] cholesterol level,[29] and

Table 4 Summary of adverse events associated with OCS use.

Adverse event	# Of studies (# of quality studies)	Adverse event	# Of studies (# of quality studies)
Fracture	28 (24)	Pain	4 (1)
Gastric condition	13 (9)	Impaired growth	3 (3)
Psychiatric condition	11 (4)	Hypertension	3 (1)
Skin condition	8 (6)	Weakness	3 (1)
Hyperglycaemia	8 (5)	Adrenal insufficiency	2 (2)
Weight gain	7 (5)	Respiratory	2 (0)
Ocular condition	6 (5)	Non-Hodgkin lymphoma	1 (1)
Cerebrovascular	6 (4)	Deep vein thrombosis	1 (0)
Cardiac condition	5 (3)	Wound dehiscence	1 (0)
Infection	4 (4)	Urinary disorder	1 (0)
Moon face	4 (3)	Menstrual disorder	1 (0)
Abnormal hair growth	4 (2)		

Quality studies are defined as those having an A, B or C grade on a scale of A–E.

Table 5 Summary of all studies identifying OCS related adverse events.

Study first author[ref]	Year	Study quality (A–E)	OCS name	OCS therapy length	Primary diagnosis	# Of patients	Patient incidence of adverse event	Placebo incidence
de Vries[12]	2007	A	n/a	n/a	n/a	191,752	60% increase in osteopathic fracture (<7.5 mg/day); 115% increase in 7.5–15 mg/day; > 30 mg/day 363% increase	No control group 14 studies have no control group
de Vries[55]	2007	A	OCS (prednisolone, dexamethasone, traimcinolone, hydrocortisone)	>4 months	Inflammatory disease	6763	Femur/hip fracture increased (crude OR 1.66, 95% CI: 1.46–1.90)	n/a
Varas-Lorenzo[24]	2007	A	Prednisolone or equivalent	Current use within last 30 days, recent use 30–180 days prior, past use >180 days	n/a	4795	Increased risk of myocardial infarction (adjusted RR = 1.71 [95% CI 1.44–2.02] for current users, adjusted RR = 1.44 [95% CI 1.34–1.83] for recent users, adjusted RR = 1.28 [95% CI 1.15–1.43] for past users	n/a
Curtis[27]	2006	B	Prednisone, prednisolone, dexamethasone, other OCS	>60 days	n/a	2446	Weight gain (70%); ≥1 AE – Weight gain, cataracts, fractures, acne, skin-bruising (90%); also found association between greater cumulative dose and increased AEs	n/a
Huiart[25]	2006	A	n/a	n/a	COPD	371	Increased risk of Acute myocardial infarction (adjusted RR = 2.01 [95% CI 1.13–3.58]) for patients w current OCS exposure, patients w past exposure also at increased risk (adjusted RR = 2.01 [95% CI 0.90–1.70)	n/a
Mortimer[56]	2006	C	n/a	90 days	Asthma; COPD	154	Increased risk of adrenal insufficiency OR 2.0 (95% CI 1.6–2.5) per course of treatment per year	n/a
Syed[57]	2006	B	n/a	n/a	Osteoporosis	37	Refractures 37.8% (RR 1.84 vs. control)	20.6%
Donnan[6]	2005	A	n/a	n/a	n/a	20,266	Higher risk of fracture (RR = 1.90, 95% CI 1.68, 2.16); 1 in 6 vertebral and 1 in 13 non-vertebral fractures attributed to OCS; women at higher fracture risk than men (RR = 5.19 [95% CI 2.15–9.16]	n/a
Kumagai[29]	2005	D	Prednisone or equivalent	>1 month	Autoimmune disease	160	Patients w hyperlipidemia (cholesterol > 280 mg/dl) have higher risk for vertebral fracture (RR = 3.1, $p = 0.032$)	No control group
Nagasawa[58]	2005	C	Prednisolone	5 years	Systemic lupus erythematosus	45	Osteonecrosis of femoral head 15 (33%) silent ONF; 5 (11%) symptomatic ONF	n/a
van Staa[20]	2005	A	n/a	n/a	n/a	191,752	7412 osteoporotic fracture (RR 1.21, 95% CI 1.04–1.42); increased RR in older patients and women	n/a

Vestergaard[13]	2005	A	Prednisolone or equivalent	n/a	Fracture	124,655	Increased risk of fracture present with >2.5 mg/day, RR increases with dose	n/a
Patel[59]	2000	D	Prednisolone	n/a	Polymorphic light eruption (PLE)	10	GI upset (1); depressed mood (1)	0
Sorensen[32]	2004	A	n/a	n/a	n/a	59,043	non-Hodgkin lymphoma (standardized incidence ratio SIR = 1.30), $p = 0.04$	n/a
Souverein[26]	2004	B	OCS (cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisone, dexamethasone, betamethasone)	n/a	Ischemic heart disease	50,656	Increased risk of any cardiovascular or cerebrovascular outcome (adjusted OR 1.25, 95% confidence interval (CI) 1.21—1.29); increased risk of heart failure (adjusted OR 2.66, 95% CI 2.46—2.87); risk of heart failure is highest with current use versus recent (adjusted OR = 1.40) or past use (adjusted OR = 1.19)	n/a
Steinbuch[14]	2004	A	n/a	>2 years	n/a	17,957	Fractures (relative risk and 95% CI): hip 1.87 (95% CI, 1.2—2.9); vertebral 2.92 (95% CI, 2.0—4.3); wrist/forearm 1.03 (95% CI, 0.8—1.4); non-vertebral 1.68 (95% CI, 1.5—1.9); any fracture 1.75 (95% CI, 1.6—1.9); for all fractures considered together, significant increase in risk ($p < 0.001$) for increased dose, duration and treatment pattern (continuous versus sporadic)	n/a
van der Voort[60]	2004	C	n/a	n/a	n/a	1680	Osteoporosis risk of 71% in women using OCS	39% Osteoporosis risk
Van Staa[15]	2003	C	Prednisone equivalent	1 year	Rheumatic, pulmonary and skin disorders	195	57 Multiple fractures, daily prednisone equivalent dose >15 mg/day increases risk (RR = 1.62)	39 Multiple fractures
Van Staa[16]	2003	A	Prednisolone	6.4 days (mean)	n/a	37,562	In children only — Fracture 22,846; increased risk for children taking ≥30 mg (RR = 1.24) and children with ≥4 courses of OCS (RR = 1.32)	14716
Blackburn[33]	2002	A	n/a	n/a	n/a	31,864	Diabetes 906	626 (inhaled CS users); 1065 (proton pump inhibitor users)
Joly[61]	2002	D	Prednisone	n/a	Bullous Pemphigoid	171	11 Patients had pneumonia, 7 acquired diabetes, 6 had cardiac failure, 4 had psychiatric symptoms, 4 experiences stroke, 6 had deep vein thrombosis, 3 had bone fracture	8 patients had pneumonia, 2 acquired diabetes, 7 had cardiac failure, 4 experienced stroke, 4 had deep vein thrombosis, 3 had bone fracture

(*continued on next page*)

Table 5 (*continued*)

Study first author[ref]	Year	Study quality (A–E)	OCS name	OCS therapy length	Primary diagnosis	# Of patients	Patient incidence of adverse event	Placebo incidence
Lazenby[62]	2002	C	Prednisone	1 week	Asthma	20	Increased oesophageal acid - pH < 4.0 at distal probe was 5.9% ± 0.9%, at proximal probe 0.8% ± 0.2%	pH < 4.0 at distal probe 2.5% ± 0.4%; proximal probe 0.3% ± 0.1%
Maltais[63]	2002	C	Prednisolone	10 days	COPD	62	Hyperglycaemia 7 (10%)	0 (0%)
Simon[51]	2002	C	Prednisone	n/a	Juvenile idiopathic arthritis	24	Impaired growth – Mean final height was −2.0 ± 1.8 expressed as the height standard deviation score for chronological age	No control group
van Everdingen[64]	2002	B	Prednisone	2 years	Rheumatoid arthritis	41	Mean body weight increase from 77 ± 19 kg to 80 ± 20 kg ($p = 0.001$) Osteoporotic fractures (8); peptic symptoms (7)	No weight gain, Osteoporotic fractures (4); peptic symptoms (3)
Van Staa[65]	2002	C	Prednisolone	5.4 years	n/a	2,891	Increased fractures meta-analysis	n/a
Walsh[17]	2002	D	Prednisolone	n/a	Chronic lung disease	117	58% had osteoporosis (a T score <−2.5); 61% had a vertebral fracture, strong relationship between dose and vertebral fracture (RR = 4.4 between highest and lowest dose quartiles), also relationship between vertebral fractures, age and smoking status	n/a
Levine[66]	2002	C	Budesonide, prednisone	n/a	Juvenile Crohn's disease	120	Hirsutisum (1/62); moon face (2/62); acne (1/62); herpetic infection (2/58); proximal myopathy (1/58); depression (5/58)	
Marcocci[67]	2001	C	Prednisone	5 months	Graves' ophthalmopathy	41	Any OCS adverse AE 35 (85%) – consisting of urinary tract infection, glucose intolerance, cushingoid features	n/a
Oinuma[68]	2001	D	n/a	12 months	Systemic lupus erythematosus	72	Osteonecrosis 32 (44%)	No control group
Van Staa[18]	2001	A	Prednisolone	7.4 months	n/a	244,235	Excess hip fractures (females; >85 y) were 1.4 cases per 100 patients per year. 47% hip and 72% vertebral fractures could be attributed to oral corticosteroid use. Among 10,000 females, 99.7 nonvertebral, 31.6 hip and 45.8 vertebral fractures can be attributed to oral corticosteroids. Increased risk associated with high dose plus female sex	n/a

Walsh[5]	2001	A	Prednisolone	6.4 years (F); 4.5 years (M)	Asthma; COPD; Fibrosing Alveolitis	367	Cataracts (18.4%); oral candidiasis (29.7%); use of H2-antagonists/ indigestion (22.6%); bruising (72.9%); muscle weakness (60%); height loss of >2.5 cm since age 25 (37.6%); back pain (54%); osteoporotic fracture (23.2%); 2 or more fractures (7.4%); Increased rate of all fractures, cataracts, bruising and muscle weakness fracture with higher cumulative dose	Cataracts (8.6%); oral candidiasis (2.7%); use of H2-antagonists/ indigestion (7.8%); bruising (10.9%); muscle weakness (19.3%); height loss of >2.5 cm since age 25 (26.3%); back pain (48.2%); osteoporotic fracture (14.7%); 2 or more fractures (3.1%)
Nishimura[69]	2000	E	Dexamethasone	n/a	Hormone-refractory prostate carcinoma	37	Hypertension (2); mental confusion (2); cataracts (1); diabetes (1)	No control group
Rothberg[28]	2000	B	n/a	n/a	n/a	1614	Hip fractures (1 F; 3 M); osteoporosis (14.1% F; 5.9% M) RR = 1.45; Women older than 45 yrs − 17.6% osteoporosis, 0.2% hip fracture; female gender and old age predictor of increased osteoporosis	Women older than 45 yrs − 12.9% osteoporosis, 0.5% hip fracture
Van Staa[70]	2000	A	n/a	28 days (median)	n/a	244,235	Nonvertebral fracture RR = 1.33; forearm fracture RR = 1.09; hip fracture RR = 1.61; vertebral fracture RR = 2.60; all fractures exhibited a dose dependant relationship	n/a
Van Staa[71]	2000	A	n/a	n/a	n/a	244,235	Nonvertebral fracture RR = 1.33 (95% confidence interval [CI], 1.29−1.38); hip fracture RR = 1.61 (1.47−1.76); forearm fracture RR = 1.09 (1.01−1.17); vertebral fracture RR = 2.60 (2.31−2.92); fractures exhibited a dose dependant relationship	n/a
Zonana-Nacach[19]	2000	C	Prednisone	>2 months	Systemic lupus erythematosus	539	Osteoporotic fractures (relative risk [RR] 2.5, 95% confidence interval [95% CI] 1.7, 3.7), symptomatic coronary artery disease (RR 1.7, 95% CI 1.1, 2.5), and cataracts (RR 1.9, 95% CI 1.4, 2.5); 1.2-fold increase in avascular necrosis (95% CI 1.1, 1.4) and stroke (95% CI 1.0, 1.5); increase in risk with each additional two month exposure	n/a

(*continued on next page*)

Table 5 (*continued*)

Study first author[ref]	Year	Study quality (A—E)	OCS name	OCS therapy length	Primary diagnosis	# Of patients	Patient incidence of adverse event	Placebo incidence
Kim[11]	1999	E	Prednisolone	4 m	Vitiligo	81	Patients experienced several OCS AEs including facial swelling (21%), weight gain (17.3%), acneiform eruption (9.9%), weight gain (4.9%), gastrointestinal disorders (6.2%), abdominal pain (4.9%), hypertrichosis (3.7%) and insomnia (2.5%); differences in AE incidence between paediatric and adult population	no control group
Dasgupta[72]	1998	C	Prednisolone	96 weeks	Polymyalgia rheumatica	25	Bruising 4 (13.3%); dyspepsia 3 (9.9%); Chest infections 4 (13.3%); urinary tract infections 1 (3.3%); ankle oedema 3 (9.9%); moon face 3 (9.9%); tremor 1 (3.3%); depression1 (3.3%); hypertension 2 (6.6%); back pain 2 (6.6%); cataract 2 (6.6%); fractures 8 (26.6%)	n/a
Sartor[73]	1998	E	Prednisone	n/a	Hormone-refractory prostate cancer	29	Myopathy (4); diabetes (1); dyspnoea (1)	No control group
Sharma[74]	1998	E	Prednisolone; betamethasone	>3 months	Alopecia areata	16	Hyper-acidity (1); headache (1); transient giddiness (1); body ache (1)	No control group
Borgna-Pignatti[75]	1997	E	Dexamethasone	6 months	Chronic idiopathic thrombocytopenia purpura	17	Fatigue (9); irritability (7); abdominal pain (2); phobias, headache, anxiety, striae rebrae, hirsutism and acne (all 1)	No control group
Campieri[76]	1997	C	Prednisolone (pred); budesonide (bud)	12 weeks	Crohn's disease	177	During study: moon face - prednisolone group 22/58, budesonide groups (both once and twice daily) 15/119; acne — pred 11/58, bud 23/119; swollen ankles — pred 3/58, bud 7/119; bruising — pred 7/58, bud 17/119; hirsutism — pred 3/58 bud 6/119; buffalo hump — pred 2/58, bud 0/119; others — pred 16/58, bud 13/119	No control group
Garbe[22]	1997	A	OCS (hydrocortisone, cortisone, prednisone, prednisolone, triamcinolone, dexamethasone, betamethasone)	n/a	Ophthalmology patients	9793	Ocular hypertension (crude OR 1.43, adjusted OR 1.41); risk increases with longer duration of OCS use and increased dose	n/a
Ginsberg[77]	1996	D	dexamethasone	48 h	Iohexol myelography	42	Insomnia (1); dyspepsia (1)	0
Howland[78]	1996	C	Prednisone	6 weeks	Allergic rhinitis	16	Adrenocortical function - mean change in 6-hour plasma cortisol levels 33.38 μg/dl ($p < 0.001$)	49.81 μg/dl

Naber[79]	1996	D	Methylprednisolone; fluocortolone	8 days	Ocular diseases	50	36% organic mood disorder, 26–34% hypomanic syndrome, 10–12% a depressive syndrome	no control group
Ziv[80]	1996	B	prednisone	>1 month	Ulcerative colitis	361	Septic surgical complications 2 of 10 (20%) low dose; 5 of 10 (50%) high dose	1 of 26 (3.8%)
Scarfone[81]	1995	D	Prednisone	Single dose	Asthma	55	Vomiting pill 10 (15%)	0 (0%)
Allen[52]	1994	C	Prednisone; 'other oral'	n/a (meta-analysis)	Asthma	810	Prednisone growth impairment ($Z = 2.137$, $p = 0.0164$, mean $r = -0.295$); 'other oral corticosteroids' ($Z = 9.107$, $p = 2.44E-18$, mean $r = -0.260$)	n/a
Blanchette[82]	1994	D	Prednisone	21 days	Childhood acute immune thrombocytopenic purpura	39	Weight gain 6% of pre-trial weight	n/a
Decramer[23]	1994	E	Methylprednisolone (17); prednisone (3); triamcinolone (1)	>6 months	COPD; asthma	21	Peripheral muscular weakness 8, greater muscle weakness positively correlated with log of average daily dose	no control group
Gurwitz[21]	1994	A	OCS (cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, betamethasone)	n/a	n/a	11,855	Estimated relative risk for hyperglycemia requiring treatment was 2.23 (95% CI, 1.92–2.59) as compared with nonusers	n/a
Saag[83]	1994	A	Prednisone	>1 year	Rheumatoid arthritis	112	Fracture 21; serious infections 14; gastrointestinal bleed or ulcer 11; cataracts 17	Fracture 8; serious infections 4; gastrointestinal bleed or ulcer 4; cataracts 5
Blanchette[84]	1993	C	Prednisone	21 days	Childhood acute immune thrombocytopenic purpura	18	Mean 3.6% weight gain of pre-trial weight; 1 incidence of each: glycosuria, epigastric discomfort, behavioural change	0
Chrousos[85]	1993	C	Prednisone	14 days	Optic neuritis	155	Sleep disturbance 70 (45%); mild mood change 53 (34%); stomach upset 64 (41%); facial flushing 16 (10%)	Sleep disturbance 30 (20%); mild mood change 24 (16%); stomach upset 37 (25%); facial flushing 3 (2%)
Olgaard[86]	1992	C	Prednisone; deflazacort	6 and 12 months	Nephrotic syndrome	29	Forearm bone decay rate 5.3%/year (PDN) and 2.0%/year (DFZ). Mandible decay rate 7.0%/year (both groups); lumbar spine 12.5%/year (PDN) and 6.8%/year (DFZ).	No control group

(*continued on next page*)

Table 5 (*continued*)

Study first author[ref]	Year	Study quality (A—E)	OCS name	OCS therapy length	Primary diagnosis	# Of patients	Patient incidence of adverse event	Placebo incidence
Ramond[87]	1992	C	Prednisolone	28 days	Severe alcoholic hepatitis	32	Psychological disturbance (1); bacterial meningitis (1)	Bacterial infection (1); gastrointestinal bleeding (1)
Sanders[88]	1992	D	Prednisone primarily	n/a	Asthma	240	Hypertension (associated with OCS withdrawal) 9	no control group
Fechner[89]	1991	E	Prednisone	Single dose	Corneoscleral wounds	100	Wound dehiscence requiring resuturing 10 (10%)	0
Piper[30]	1991	B	Cortisone; hydrocortisone; prednisolone; prednisone; meprednisone; triacinolone; paramethasone acetate; dexamethasone; betamethasone	n/a	Gastric/duodenal ulcer; upper gastrointestinal haemorrhage	1,415	Peptic ulcer RR = 2.0 (95% CI, 1.3 to 3.0). Risk increased in concurrent NSAID/corticosteroid use to 4.4 (CI, 2.0—9.7). RR for corticosteroid users not receiving NSAIDs was 1.1 (CI, 0.5—2.1).	n/a
Anderson[90]	1990	C	Prednisone; prednisolone	3 weeks (tapered 14—21 days)	Corrosive oesophageal injury	31	Brain abscess requiring open drainage 1	0

Table 6 Adverse events associated with OCS use in children.

First author[ref]	Year	Primary diagnosis	# Of patients	Adverse event	Patient incidence	Control incidence
Van Staa[16]	2003	n/a	37,562	Fractures	22,846	14,716
Simon[51]	2002	Juvenile idiopathic arthritis	24	Impaired growth	During OCS therapy, height stunted -2.7 ± 1.5 st devs; post-OCS -2.0 ± 1.8	
Levine[66]	2002	Juvenile Crohn's disease	120	Hirsutism	1/62	n/a
				Moon face	2/62	
				Acne	1/62	
				Herpetic infection	2/58	
				Proximal myopathy	1/58	
				Depression	5/58	
Kim[11]	1999	Vitiligo	38	Facial swelling	4/38	n/a
				Abdominal pain	4/38	
				Weight gain	3/38	
				Hypertrichosis et al.	3/38	
Sharma[74]	1998	Alopecia areata	16	Hyper-acidity	1/16	n/a
				Headache	1/16	
				Transient giddiness	1/16	
				Body ache	1/16	
Scarfone[81]	1995	Asthma	55	Vomiting	10 (15%)	0 (0%)
Allen[52]	1994	Asthma	810	Impaired growth	Prednisone vs. control, $p = 0.0164$; other OCS vs control, $p = 2.44E\text{-}18$	
Blanchette[82]	1994	Acute immune thrombocytopenic purpura	39	Weight gain	6%	1%, 2%
Blanchette[84]	1993	Acute immune thrombocytopenic purpura	18	Weight gain	3.6%	0
				Glycosuria	1	0
				Epigastric discomfort	1	0
				Behavioural change	1	0
Sanders[88]	1992	Asthma	240	Hypertension	9	n/a

concomitant drugs.[30] Treatment history was defined by current, recent or past use of OCS, although the exact definition of recent and past use varied somewhat between studies. It was reported that recent users are the most likely to develop fractures compared to current and past users[16] but current users have a higher incidence of fracture compared to past users.[6,16] For myocardial infarction, current use imparted the highest risk (1.71 RR) with reduced risk for recent users (1.44 RR) and past users (1.28 RR) experiencing a progressively lower level of increased risk.[24] Similar increased risk was reported by Huiart et al. for myocardial infarction, who found current OCS users at a relative risk of 2.01 and past users at a risk of 1.24 compared to controls as well as Souverein et al. who reported a relative risk for heart failure of 2.66 for current OCS users compared to 1.40 for recent users and 1.19 for previous users. For ocular hypertension and open-angle glaucoma, current use led to an odds ratio of 1.41 compared to 1.18 for recent use and 0.92 for past use.[22] Age was found to increase incidence of fractures in both men and women[20,14] as well as osteoporosis,[28] but this was particularly prevalent in women, who had a 14 fold increase in hip fractures between the age ranges of 45–54 and 85+[18] and were also more prone to osteoporosis.[28] OCS treatment was also found to have more adverse effects on women than men with increased incidence of fractures throughout the body in women ranging from 164% (vertebral)-316% (hip)[18] which was independently confirmed by an additional study of vertebral fractures in women and men.[6] Sporadic treatment was found to impart a reduced risk compared to continuous treatment ($p < 0.001$),[14] as was cholesterol levels lower than 280 mg/dl ($p = 0.032$),[29] and concomitant aspirin was found to increase the risk of peptic ulcers more than 15 times nonusers of either drug.[29] Smoking (number of pack years) was the only variable that was found to reduce the risk of vertebral fracture (RR = 0.50 for >20 pack years).[17]

Although the effects of treatment duration, treatment history, age and gender as well as other variables are potentially less robust than the dose–response relationship, it is clear that these factors play a role in the occurrence of many of the adverse events related to OCS.

Economic studies

One study was identified that examined the economic impact of OCS on osteoporosis and bone fractures as well as the cost-effectiveness of treating osteoporosis with biphosphonate therapy.[31] Although the cost of fracture increased considerably with age, the average cost for care of an OCS related hip fracture was £10,761. The cost was £1976 for a vertebral fracture and £863 for a forearm

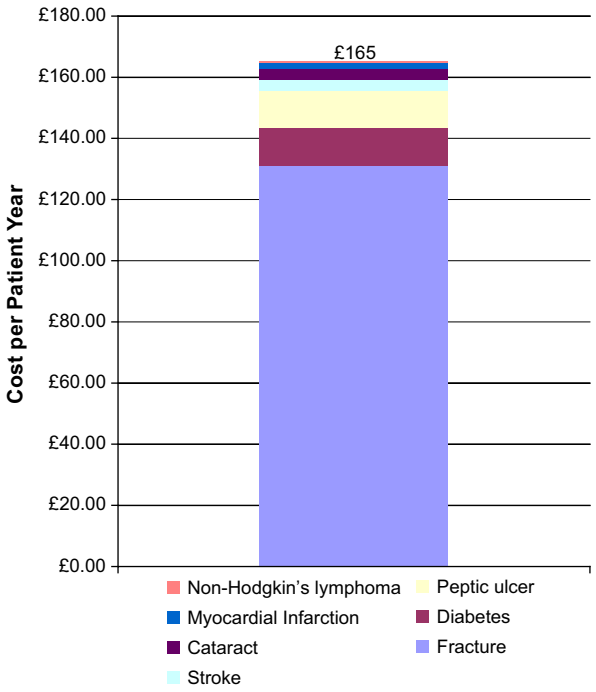

Figure 2 Cost per Patient Year of OCS Related AEs.

fracture. Not included in these amounts are annual costs for analgesic drugs and nursing home admission necessitated by these fractures. To date, no other economic analyses have reported the financial burden for the patient, the health care system, or society due to other adverse events associated with OCS use.

Cost analysis

Data on RRs was reported for seven different clinically discreet AEs; fracture, cataract, diabetes, peptic ulcer, stroke, myocardial infarction and non-Hodgkin's lymphoma.[24,6,32,33,19,30] These were used as the basis for a cost analysis. The incidences of these events in the general population of the UK were identified[34–43] allowing calculation of the estimated total number of events caused by OCS. The cost per event or per year of treatment was then applied[44–50] to estimate the annual economic burden attributable to OCS AEs. For all AEs summed together, this amounted to £165 per OCS treated patient per year, with fractures representing the most costly of the 7 AEs (Fig. 2). A summary of the relative risks, general UK population incidence and UK costs for these 7 AEs can be found in Table 7.

The cost of managing the 7 °C S-related AEs across the UK population was estimated using this £165 per patient cost. Controlling for the incidence of these events within the untreated population and assuming that 0.9% of the UK population is receiving OCS treatment at any time,[1] this amounts to 14,444 AEs directly related to OCS therapy. Estimated related costs are £84.2 million annually. Most of this expenditure falls upon the NHS and could be prevented by using OCS sparing medications and clinical practices. In comparison, the NHS spends approximately £996 million to treat asthma each year (Asthma UK), which is equivalent to £162 per adult. Asthma is the condition that was most frequently reported by studies examined to have OCS related side effects ($n = 7$).

Discussion

Our literature search revealed 63 studies identifying 21 different clinical categories of adverse events in 15 different patient groups, thereby confirming the diverse nature of adverse events caused by OCS and their impact on a wide variety of patient groups. Fractures were the most commonly reported AE and they were also the most costly of AEs included in our economic analysis, costing an average of £131 per patient taking OCS per year. Of the studies identifying dose–response, all reported the maximum risk of AEs with the highest dose of OCS. A relationship between several other factors such as duration of use, treatment history, age and gender was also examined in a few studies, confirming there are many variables that help define the risk of AEs for individual patients taking OCS.

One benefit of this review is that it indirectly compared data on the various factors influencing the risk for adverse events including dose, gender, age, treatment duration, medical and treatment history. With the exception of Souverenin et al. who did not find a clear relationship between increasing dose and increasing risk of AEs, most studies agreed that these factors related to enhanced risk for AEs.

Table 7 Data informing the cost per AE analysis.

Adverse event	Relative risk for patients taking OCS	Study quality (A–E) of RR Data	UK population incidence	2007 Cost per episode/yr	Cost per patient taking OCS
Fracture	1.95	A	0.0211	£6,541.12	£131.12
Diabetes	2.31	A	0.0038	£2,519.86	£12.39
Peptic ulcer	2.00	B	0.0012	£10,163.28	£12.11
Stroke	1.20	C	0.0026	£7,148.33	£3.67
Cataract	1.90	C	0.0043	£890.67	£3.47
Myocardial Infarction	1.42	A	0.0039	£1,369.95	£2.27
Non-Hodgkin's lymphoma	1.30	A	0.0002	£8,210.21	£0.41
				Total	£165.44

Paediatric patients taking OCS were specifically examined and besides demonstrating many of the adverse events present in adults, had the additional burden of impaired growth[51,52] and were more susceptible to certain AEs than adults,[11] therefore suggesting a particularly strong need for OCS sparing treatments in this population.

Not only do the identified adverse events have a strong negative impact on the health of patients, but they also have economic and societal consequences as well. The analysis performed here indicated that for the 6 °C S-related AEs that had RRs reported in the literature, the annual cost per patient attributable to that OCS related AE was estimated at £165. This is certain to be an underestimation of the economic burden, because not all AEs had sufficient data on relative risk to be included, and in particular, many of the particularly costly AEs were not included. For example, in Denmark, the four most costly illnesses are (in descending order) mental illness, cardiovascular disease, digestive system disorders, and musculoskeletal disorders.[53] OCS is a risk factor for all 4 of these conditions, but only digestive system disorders (i.e. peptic ulcers) were included in our cost analysis. Thus, a reduction in OCS dependence and OCS usage could have a strong economic impact, greater than our current estimate, by reducing the health care burden for OCS-managed patients.

Economic impact of OCS adverse events has only been directly reported for fractures.[31] However, while the direct economic impact of treating other AEs related to OCS hasn't been established, it can be inferred through published costs of treating these conditions in the general public. For example, diabetes (RR 2.31[33]) care added $10,683 to per person annual health costs in the US (American Diabetes Society, 2003), and the yearly per patient cost for non-Hodgkin's lymphoma (RR 2.68[32]) was estimated to be between $4260 and $70,452 depending on severity.[54] Although not all costs for treating other adverse events associated with OCS will be as excessive as these (e.g. skin conditions, weight gain and moon face might cost less) and some adverse events have lower overall incidence than others, the cumulative cost for treatment of all potential adverse events is likely to be high. Although the cost analysis performed here is specific to the UK due to the availability of data, it would be expected that the cost implications of OCS use in other Western health care systems would be comparable, especially given the widespread use of OCS to treat several diseases.

Although only 4 studies included in the analysis were large prospective clinical trials, a large proportion of studies (28) were chart reviews with an average 58,620 patients each, thus sufficiently large to identify adverse events in a more natural setting. A shortcoming is that most trials identified in the literature investigated the presence of only a single adverse events or adverse events within the same categories, with only a few studies (16 out of 63 studies) that could directly compare the incidence of different types of adverse events in the same population and with the exact same treatment conditions (i.e. dose, duration of OCS therapy), making a direct comparison of incidence somewhat less meaningful.

This review highlights the need for further work in terms of studies to identify the comprehensive risk of adverse events in patients taking OCS, and in identifying the cost burden that these adverse events represent. It is expected that these data will further emphasize the need to develop steroid-replacement therapies which will make it possible to avoid these burdensome adverse events.

Conflict of interest

The authors have no conflict of interest to disclose in relation to this work.

Acknowledgements

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Appendix I Embase, Medline and Cochrane Library Inc. Search Strategies

Search Name: Oral steroids_All pops
Comments: 050407
Save Date: 2007-04-05 15:49:29
Database: Cochrane Library, Inc. <to 2007>
Search Strategy:
————————————————————————————————
ID Search
#1 MeSH descriptor Asthma explode all trees
#2 (asthma*):ti
#3 (#1 OR #2)
#4 MeSH descriptor Prednisolone explode all trees with qualifier: ae
#5 MeSH descriptor Prednisone explode all trees with qualifier: ae
#6 MeSH descriptor Betamethasone explode all trees
#7 MeSH descriptor Dexamethasone explode all trees with qualifier: ae
#8 (prednisolon* or prednison* or methylprednisolone or betamethason* or dexamethason*):ti
#9 corticosteroid*:ti
#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Administration, Oral explode all trees
#12 ((oral):ti not ''oral health'':ti) OR (systemic*:ti near *cortico*:ti)
#13 (#11 OR #12)
#14 (((oral or systemic) near (cortico* or *steroid*)) or ''OCS''):ti
#15 ((#10 AND #13) OR #14)
#16 Any MeSH descriptor with qualifier: AE
#17 ((advers* or side* or negativ* or detriment*) next (outcome* or effect*)):ti
#18 MeSH descriptor Hypertension explode all trees with qualifier: CI
#19 MeSH descriptor Myocardial Infarction explode all trees with qualifier: CI
#20 MeSH descriptor Osteoporosis explode all trees with qualifier: ci
#21 MeSH descriptor Cataract explode all trees with qualifier: ci

#22 MeSH descriptor Wound Healing explode all trees with qualifier: DE
#23 MeSH descriptor Atrial Fibrillation explode all trees with qualifier: ci
#24 MeSH descriptor Adrenal Insufficiency explode all trees with qualifier: ci
#25 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#26 (#15 AND #25)
#27 (#26), from 1990 to 2007
#28 MeSH descriptor Postoperative Complications explode all trees
#29 (#27 AND NOT #28)

Database: EMBASE <1988 to 2007 Week 13>
Search Strategy:
————————————————————————————

1 *Glucocorticoids/ae (1319)
2 exp *Prednisolone/ae (1261)
3 exp *Prednisone/ae (2204)
4 exp *Methylprednisolone Hemisuccinate/ae or exp *Methylprednisolone/ae (1130)
5 exp *Betamethasone/ae (277)
6 exp *Dexamethasone/ae (1311)
7 or/1—6 (6748)
8 exp administration, oral/or ((oral$ or systemic$) adj3 $cortico$).ti. (187734)
9 7 and 8 (1335)
10 *Glucocorticoids/po (302)
11 *corticosteroid/po (1345)
12 10 or 11 (1640)
13 8 or 12 (189259)
14 exp *Prednisolone/ae (1261)
15 exp *Prednisone/ae (2204)
16 exp *Methylprednisolone Hemisuccinate/ae or exp *Methylprednisolone/ae (1130)
17 exp *Betamethasone/ae (277)
18 exp *Dexamethasone/ae (1311)
19 (prednisolon$ or prednison$ or methylprednisolone or betamethason$ or dexamethason$).ti. (11948)
20 ($cortico$ or $steroid$ or glucocorticoid$).ti. (51163)
21 or/14—20 (64988)
22 13 and 21 (6170)
23 exp *side effect/(13352)
24 exp *hypertension/si (1580)
25 exp *myocardial infarction/si (599)
26 exp *osteoporosis/si (1454)
27 *corticosteroid induced osteoporosis/(163)
28 exp *cataract/si (242)
29 exp *Wound Healing/si (21)
30 exp *atrial fibrillation/si (119)
31 exp *Adrenal Insufficiency/si (111)
32 exp *fractures/si (288)
33 (''steroid-induced'' or ''steroid induced'').ti. (468)
34 ((advers$ or side$ or negativ$ or detriment$ or ''long term'') adj2 (outcome$ or effect$)).ti. (20213)
35 or/23—34 (37427)
36 22 and 35 (410)
37 9 or 36 (1613)
38 (inhaled not oral$).ti. (6439)
39 37 not 38 (1566)
40 letter.pt. (343547)
41 letter/(351404)
42 editorial.pt. (175487)
43 historical article.pt. (0)
44 case report$.pt. (0)
45 case study/(2916)
46 exp animal/not human/(78072)
47 nonhuman/(2390477)
48 anecdote.pt. (0)
49 commentary.pt. (0)
50 case study.pt. (0)
51 exp Animal Studies/(780369)
52 Animals, Laboratory/(3220)
53 note.pt. (209260)
54 comment.pt. (0)
55 exp experimental animal/(86279)
56 exp animal experiment/(780369)
57 exp animal model/(395109)
58 exp rodents/or exp rodentia/(1057616)
59 exp rodent/(1057616)
60 Case Report/(701604)
61 short survey/(242517)
62 short survey.pt. (198350)
63 note/(209074)
64 or/40—63 (3892760)
65 review.pt. or review.ti. (760320)
66 (systematic$ or evidence$ or methodol$ or method$ or quantitativ$ or analys$ or assessment$).ti,sh,ab. (2914146)
67 65 and 66 (248681)
68 meta-analysis.pt. (0)
69 Meta-Analysis/(29549)
70 ''systematic review''/(16237)
71 (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab. (16614)
72 ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh. (62685)
73 ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. (14752)
74 or/67—73 (297628)
75 (review.pt. or review.ti.) not 74 (507494)
76 37 not 64 (1133)
77 76 not 75 (1018)
78 limit 77 to yr = ''1990—2007'' (836)
79 exp Postoperative Complication/(175627)
80 exp *Malignant Neoplastic Disease/(427773)
81 exp *Antiemetic Agent/(20282)
82 screening/(27765)
83 or/79—82 (643045)
84 78 not 83 (490)
85 exp Regression Analysis/(61894)
86 exp ''Analysis of Variance''/(13058)
87 Factor Analysis, Statistical/(7409)
88 exp survival analysis/(183826)
89 confounding.ab. (14608)
90 (regression adj2 analys$).ab. (58963)
91 (regression adj2 model$).ab. (21801)
92 (factor$ or variable$).ti,ab. (1113139)
93 (relative adj2 risk$).ab. (27378)
94 risk$ factor$.ti,ab. (143311)

95 risk/(19386)
96 risk factor/(188569)
97 logistic models/(16145)
98 risk assessment/(140995)
99 risk management/(8953)
100 exp multivariate analysis/(62519)
101 ((multivariable or multivariate or multi-varia$) adj2 analys$).mp. (59422)
102 or/85–100 (1512890)
103 84 and 102 (136)
104 84 not 103 (354)
105 economics/(4486)
106 exp ''costs and cost analysis''/(100562)
107 economic value of life/(24360)
108 exp economics, hospital/(185050)
109 exp economics, medical/(185050)
110 economics, nursing/(8937)
111 economics, pharmaceutical/(882)
112 exp models, economic/(16145)
113 exp ''fees and charges''/(7369)
114 exp budgets/(6535)
115 (economic$ adj2 evaluat$).ti,ab. (3346)
116 ec.fs. (1890755)
117 (cost or costs or costed or costin$).ti,ab. (123248)
118 (economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab. (60558)
119 (budget$ or (cost$ adj2 (benefit$ or Utilit$ or effective$ or model$))).ti,ab. (45603)
120 (value adj2 money).ti,ab. (338)
121 or/105-120 (2179771)
122 (84 and 121) not 103 (88)
123 84 and 102 (136)
124 123 or 122 (224)

Database: Ovid MEDLINE(R) <1950 to March Week 4 2007>
Search Strategy:
————————————————————

1 *Glucocorticoids/ae (1956)
2 exp *Prednisolone/ae (1312)
3 exp *Prednisone/ae (1016)
4 exp *Methylprednisolone Hemisuccinate/ae or exp *Methylprednisolone/ae (497)
5 exp *Betamethasone/ae (309)
6 exp *Dexamethasone/ae (627)
7 or/1–6 (4627)
8 exp administration, oral/or (oral$ or systemic$).ti. (209662)
9 7 and 8 (367)
10 *Glucocorticoids/(16366)
11 exp *Prednisolone/(15428)
12 exp *Prednisone/(8259)
13 exp *Methylprednisolone Hemisuccinate/or exp *Methylprednisolone/(6261)
14 exp *Betamethasone/(3107)
15 exp *Dexamethasone/(16096)
16 (prednisolon$ or prednison$ or methylprednisolone or betamethason$ or dexamethason$).ti. (21691)
17 ($cortico$ or $steroid$ or glucocorticoid$).ti. (96949)
18 or/10–17 (129868)
19 8 and 18 (4579)
20 exp hypertension/ci (6602)
21 exp myocardial infarction/ci (1945)
22 exp osteoporosis/ci (1758)
23 exp cataract/ci (1546)
24 exp Wound Healing/de (8185)
25 exp atrial fibrillation/ci (373)
26 exp Adrenal Insufficiency/ci [Chemically Induced] (429)
27 exp spinal fractures/ci (44)
28 (''steroid-induced'' or ''steroid induced'').ti. (717)
29 ((advers$ or side$ or negativ$ or detriment$ or ''long term'') adj2 (outcome$ or effect$)).ti. (29676)
30 or/20–29 (50700)
31 19 and 30 (239)
32 9 or 31 (518)
33 letter.pt. (586160)
34 letter/(586160)
35 editorial.pt. (201058)
36 historical article.pt. (237644)
37 case report$.pt. (1290493)
38 case study/(1290493)
39 exp animal/not human/(3165380)
40 nonhuman/(0)
41 anecdote.pt. (0)
42 commentary.pt. (0)
43 case study.pt. (0)
44 exp Animal Studies/(0)
45 Animals, Laboratory/(8396)
46 note.pt. (0)
47 comment.pt. (326288)
48 exp experimental animal/(263785)
49 exp animal experiment/(0)
50 exp animal model/(263785)
51 exp rodents/or exp rodentia/(2046542)
52 exp rodent/(0)
53 Case Report/(0)
54 or/33–52 (5727308)
55 review.pt. or review.ti. (1330067)
56 (systematic$ or evidence$ or methodol$ or method$ or quantitativ$ or analys$ or assessment$).ti,sh,ab. (3951796)
57 55 and 56 (333727)
58 meta-analysis.pt. (15000)
59 Meta-Analysis/(7343)
60 ''systematic review''/(0)
61 (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab. (17693)
62 ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh. (41542)
63 ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. (19217)
64 or/57–63 (374234)
65 (review.pt. or review.ti.) not 64 (994516)
66 32 not 54 (310)
67 66 not 65 (275)
68 limit 67 to yr = ''1990–2007'' (170)
69 from 68 keep 39 (1)
70 exp *Asthma/(63988)
71 asthma$.ti. (53180)
72 70 or 71 (65495)

73 *Glucocorticoids/(16366)
74 exp Prednisolone/(35287)
75 exp Prednisone/(28334)
76 exp Methylprednisolone Hemisuccinate/or exp Methylprednisolone/(12695)
77 exp Betamethasone/(4971)
78 exp Dexamethasone/(35579)
79 (prednisolon$ or prednison$ or methylprednisolone or betamethason$ or dexamethason$).ti. (21691)
80 corticosteroid$.ti. (16070)
81 adrenal cortex hormones/tu (18934)
82 Anti-Asthmatic Agents/(4917)
83 ((oral adj3 (cortico$ or $steroid$)) or ''OCS'').ti. (746)
84 exp administration, oral/or oral$.ti. (159112)
85 or/73–81 (133282)
86 (85 and 84) or 83 (4124)
87 ae.fs. (942818)
88 ((advers$ or side$ or negativ$ or detriment$) adj2 (outcome$ or effect$)).ti,ab. (204637)
89 exp hypertension/ci (6602)
90 exp myocardial infarction/ci (1945)
91 exp osteoporosis/ci (1758)
92 exp cataract/ci (1546)
93 exp Wound Healing/de (8185)
94 exp atrial fibrillation/ci (373)
95 exp Adrenal Insufficiency/ci [Chemically Induced] (429)
96 or/87–95 (1084944)
97 72 and 86 and 96 (167)
98 letter.pt. (586160)
99 letter/(586160)
100 editorial.pt. (201058)
101 historical article.pt. (237644)
102 case report$.pt. (1290493)
103 case study/(1290493)
104 exp animal/not human/(3165380)
105 nonhuman/(0)
106 anecdote.pt. (0)
107 commentary.pt. (0)
108 case study.pt. (0)
109 exp Animal Studies/(0)
110 Animals, Laboratory/(8396)
111 note.pt. (0)
112 exp experimental animal/(263785)
113 exp animal experiment/(0)
114 exp animal model/(263785)
115 exp rodents/or exp rodentia/(2046542)
116 exp rodent/(0)
117 Case Report/(0)
118 or/98–117 (5689582)
119 review.pt. or review.ti. (1330067)
120 (systematic$ or evidence$ or methodol$ or method$ or quantitativ$ or analys$ or assessment$).ti,sh,ab. (3951796)
121 119 and 120 (333727)
122 meta-analysis.pt. (15000)
123 Meta-Analysis/(7343)
124 ''systematic review''/(0)
125 (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab. (17693)
126 ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh. (41542)
127 ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. (19217)
128 or/121–127 (374234)
129 (review.pt. or review.ti.) not 128 (994516)
130 97 not (129 or 118) (138)
131 limit 130 to yr = ''1990–2007'' (96)
132 68 not 131 (146)

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