BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015905
Article Type:	Research
Date Submitted by the Author:	09-Jan-2017
Complete List of Authors:	Bénard-Laribière, Anne; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219 Pariente, Antoine; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale Pambrun, Elodie; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219 Bégaud, Bernard; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale Fardet, Laurence; EA 7379, Université Paris Est Créteil (UPEC), CHU Henri Mondor, Service de Dermatologie Noize, Pernelle; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale, CIC Bordeaux CIC1401
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	glucocorticoids, pharmacoepidemiology, drug utilization, insurance health reimbursement

Use of oral glucocorticoids in adults: a population-based study

Anne Bénard-Laribière[1], Antoine Pariente[1,2], Elodie Pambrun[1], Bernard Bégaud[1,2], Laurence Fardet[4,5], Pernelle Noize[1,2,3]

Affiliations:

[1]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, F-33000 Bordeaux, France

[2]CHU Bordeaux, Service de Pharmacologie Médicale, F-33000 Bordeaux, France

[3]CIC Bordeaux CIC1401, F-33000 Bordeaux, France

[4]EA 7379, Université Paris Est Créteil (UPEC), F-94000 Créteil, France

[5]CHU Henri Mondor, Service de Dermatologie, F-94000 Créteil, France

Correspondence to: Anne Bénard-Laribière, Service de Pharmacologie Médicale, Hôpital Pellegrin, CHU, F-33076 Bordeaux cedex, France, anne.benard@u-bordeaux.fr, Phone +33 557571560, Fax +33 557574671

Word count: 3,196

ABSTRACT

Objectives: To study trends in use of oral glucocorticoids (GCs) among adults, characteristics of oral GC initiators and therapeutic behaviour associated with their prescription.

Design: First, a cross-sectional study repeated yearly was performed from 2007 to 2014 in a nationwide representative sample. Second, characteristics of initiators and patterns of GC therapy during the year following treatment initiation were described in a cohort of patients who began GC between 2007 and 2013.

Setting: Population-based study using data from the French reimbursement healthcare system (covering approximately 90% of the population) in patients aged ≥18 years.

Results: Over the study period, the prevalence of oral GC use ranged from 14.7% [95%CI: 14.6-14.8%] to 17.1% [17.0-17.2%] with a significant increase of 14.1% [+13.5 to +14.8%]. The 2007-2013 cohort of oral GC initiators comprised 206,759 individuals. Oral GC use was mostly short-term (68% of unique reimbursement) and more than half of short-term users took concurrent antibiotics or respiratory/otologic drugs. Chronic users (≥6 reimbursements/year) represented 1.8% (n=3,789) of the cohort. The proportion of chronic users with comorbidities likely to be worsened by GC use (diabetes, psychotic disorders, osteoporosis) was 25%. Among patients at increased risk of osteoporosis, 62% received specific prevention/monitoring measures and only 27% had a biphosphonate. Half of chronic oral GC users had a concurrent reimbursement of a proton pump inhibitor in the absence of NSAID use.

Conclusions: Oral GC use was highly widespread and increased among adults from 2007 to 2014. The overwhelming short-term use mainly concerned the growing use of unjustified prescriptions rather than situations with a favourable benefit/risk ratio. For chronic users, our findings plead for the development of interventions designed to improve monitoring with regard to the frequent comorbidities at risk and inappropriate prescribing of preventive therapeutic measures.

Strengths and limitations of this study

- The main strength is that it is representative of the general population owing to the data source, a healthcare insurance database with exhaustive recording of reimbursements and hospitalizations.

- A limitation is that the database does not include direct information on medical indications, which could be derived from data on chronic diseases, hospitalizations and concurrent drugs.
- Altogether, this population-based study provides a description of oral glucocorticoid (GC) use and trends in adults over an 8-year period from 2007 to 2014.

INTRODUCTION

Oral glucocorticoids (GCs) have been used for more than 60 years for their substantial anti-inflammatory and immunosuppressive effects in several acute and chronic disorders, both for reducing disease activity and pain.[1] However, their use is limited by the occurrence of adverse reactions related to their pharmacological properties that are mainly to be feared with higher dosages or long-term use. These associated risks include infections, osteoporosis and fractures, hyperglycaemia, neuropsychiatric disorders and muscle atrophy. Recommendations on the management of GC therapy based on expert consensus are available for the prevention of GC-induced osteoporosis;[2-4] regarding other significant adverse reactions, advice on pre-treatment and treatment monitoring have been issued [5, 6] but no consensual recommendations exist.

Besides these well-known adverse consequences, the relevance of some other potential adverse reactions is debated such as the impact on electrolyte homeostasis due to mineralocorticoid effects or the risk of peptic ulcer. While potassium loss seems negligible in practice,[7] some physicians persist in prescribing potassium supplementation which, in some situations, may carry a risk of marked hyperkalaemia.[8] Similarly, despite the literature suggesting no benefit from proton pump inhibitors (PPIs) prophylaxis in patients taking systemic GCs without concomitant non-steroidal anti-inflammatory (NSAID) use,[9, 10] many prescribers still consider GCs as a cause of upper-gastrointestinal complications and systematically add PPIs to their prescriptions.[11]

Few studies have reported the use of oral GCs in the general population, and short-term use has rarely been quantified as it is considered safe. This population-based study aimed at describing trends in the use of oral GCs among adults, the characteristics of GC initiators and the prescription behaviour associated with GC therapy.

METHODS

Data source

The study was conducted using the French reimbursement database (*Echantillon Généraliste de Bénéficiaires*, EGB). The EGB is a representative sample of the population covered by the national healthcare insurance system (approximately 90% of the whole population, irrespective of socio-

economic status) obtained by 1/97th random sampling with stratification on sex and age. For all beneficiaries, it consists of the exhaustive recording of drug reimbursements, hospitalization data (diagnoses and dates), and the existence of certain chronic diseases (*Affections de Longue Durée*, ALD, an administrative status allowing full reimbursement of health care for a given condition; *e.g.* diabetes, cancer, psychosis). Details on the EGB database have been described elsewhere.[12, 13]

Study design

Cross-sectional study

In order to study temporal trends in the use of GCs, a cross-sectional study was repeated yearly among the population aged ≥18 years, from January 1st 2007 to December 31st 2014. All individuals who had at least one reimbursement of an oral GC (i.e., betamethasone, dexamethasone, methylprednisolone, prednisolone, and prednisone) were identified for each year studied.

Cohort study

To study characteristics of GC users and therapeutic behaviour associated with the prescription, a cohort of oral GC initiators was identified. GC initiators were defined as an incident reimbursement of oral GC between January 1st 2007 and 31st December 2013, without any in the preceding year. This definition was retained to ensure incident use was identified in a conservative manner even if other definitions can be found in the literature (e.g. prescription-free, 90-day [14] or 6-month period [15, 16]). The index date was the date the incident GC was reimbursed. Each GC initiator was followed until one year since index date, the date of death, or the end of data availability in the database, whichever came first.

Characteristics of GC initiators: GC initiators were described in terms of age, sex, and concurrent drugs reimbursed at index date. Comorbidities which may represent situations at risk in the event of GC use (*i.e.* diabetes, psychotic disorders, and osteoporosis) were described, as were chronic disorders constituting recognized indications for GC therapy: rheumatic diseases (e.g. rheumatoid arthritis, polymyalgia rheumatica/giant cell arteritis, lupus and vasculitis), obstructive pulmonary

diseases (*i.e.* asthma, chronic obstructive pulmonary disease, and chronic respiratory failure), inflammatory bowel diseases (*i.e.* Crohn's disease and ulcerative colitis) and multiple sclerosis. Comorbidities and indications for oral GC treatment were identified using data from diagnoses related to hospital stays or chronic diseases (ALDs), and medication reimbursement data in the 12-month period preceding the patient's index date.

Therapeutic behaviour associated with the prescription of GCs: Over the year following GC treatment initiation, we scrutinized two types of preventive measures: (i) those that should be systematically considered such as prevention/monitoring of osteoporosis among individuals at increased risk of osteoporosis; and (ii) those for whom no consensus exists and/or that might be inappropriate (potassium supplementation without serum potassium assay, and proton pump inhibitors (PPI) prophylaxis without concurrent NSAID or aspirin use).

To assess the prevention and monitoring of osteoporosis, individuals at increased risk of GC-induced osteoporosis were defined as those who had at least six reimbursements of GCs during the 12-month period following the index date and: (i) were aged 70 years and over, or (ii) had a past history of untreated osteoporosis during the 12 months preceding the index date. Measures for prevention/monitoring of osteoporosis among these individuals were identified by at least one of the following criteria: (i) bone mineral density measurement (at least one reimbursement for dual-energy X-ray absorptiometry, DXA), or (ii) prescription of drugs indicated for osteoporosis management (at least one reimbursement for calcium, vitamin D, bisphosphonates, denosumab, raloxifene, teriparatide, strontium ranelate, calcitonin).

For non-consensually recommended measures, potentially inappropriate potassium supplementation was defined as at least one concurrent reimbursement of oral GC and potassium supplements without any serum potassium assay during the two preceding weeks. *A priori* inappropriate ulcer prophylaxis was defined as at least one concurrent reimbursement of oral GC and PPI in the absence of NSAID or aspirin at the same date.

Data analysis

Trends in use of oral GCs

The annual prevalence of GC use was defined as the proportion of GC users per 100 individuals for the corresponding year. It was first calculated for GCs overall and then by considering each GC individually. All prevalence estimates were further stratified according to the number of GCs reimbursed per year (1, 2 to 5, ≥6), and by sex and age (five categories according to age on January 1st in each year: 18-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years), and were quantified together with their 95% two-sided confidence intervals (95%CIs). To study trends in prevalent use over the study period, relative changes in prevalence of use were estimated by using the year 2007 as reference. Relative change estimates, quantified together with their two-sided 95%CI, were calculated using the percentiles bootstrap method.

Characteristics of GC initiators and therapeutic behaviour associated with prescription of GCs

All parameters were examined overall and stratified according to the number of oral GC reimbursements (consecutive or not) during the 12-month period following the index date, in users who had a unique reimbursement (hereafter termed *short-term users*), 2 to 5 reimbursements (*mid-term users*), and ≥6 reimbursements (*long-term users*). Measures for the prevention of osteoporosis were examined only for individuals with an increased risk of osteoporosis as defined above.

All analyses were performed using SAS® software (SAS Institute, version 9.4, North Carolina, USA).

RESULTS

Trends in use of oral GCs from 2007 to 2014

Of the 382,572 individuals included in the study in 2007, 56,126 had at least one reimbursement of an oral GC: the prevalence of GC use was 14.7% [95%CI: 14.6-14.8%] in 2007. It was 17.1% [17.0-17.2%] in 2014, corresponding to a 14.1% increase [+13.5 to +14.8%] compared to 2007 (Figure 1). This rise was more pronounced in individuals aged 50-59 years (+18.4% [+17.0 to +20.0%]) and 60-69 years (+19.7% [+17.9 to +21.5%]). It mostly concerned prednisolone (+21.6% [+20.8 to +22.3%]), the most used GC over the study period, irrespective of age and sex. The

prevalence of use was higher among women whatever their age, the highest value being observed in those aged 50-59 years (21.9% in 2014 [21.4 to 22.3%]). Concerning the number of GCs reimbursed per year, the prevalence of unique reimbursement slightly increased from 10.3% in 2007 to 11.8% in 2014 (+12.7% [+11.8 to +13.5%]). The proportion of individuals who had 2 to 5 reimbursements per year rose from 3.8% to 4.6% (+18.6% [+17.4 to +19.9%]). Conversely, the percentage of individuals with ≥6 reimbursements per year remained stable and ranged between 0.6% and 0.7% (+7.9% increase [+3.8 to +11.8%] compared to 2007). Figures S1 and S2, available in the online Supplementary File, present the results according to sex and age, and for each GC individually.

Characteristics of GC initiators

The 2007-2013 cohort of GC initiators comprised 206,759 individuals; 58.0% were women and median age was 45 years (interquartile range, IQR: 32-59). More than two thirds of initiators (67.6%) had a unique reimbursement of GC over the year following treatment initiation (short-term users). Mid-term users represented 30.6% of the study cohort and long-term users 1.8%. Compared with short- and mid-term users, long-term users were more likely to be older (median age 63 years, IQR: 49-76); one quarter (24.5%) had at least one comorbidity at treatment initiation that was likely to increase the risk of adverse drug reaction in the event of GC use (diabetes: 12.1%; osteoporosis: 11.0%; psychotic disorders: 3.6%). Recognized GC indications were identified in 61.1% of long-term users. Among these potential indications, obstructive pulmonary diseases (26.2%), rheumatic diseases (12.1%) and inflammatory bowel diseases (3.3%) were the most frequent, and nearly 32% of these individuals had a cancer (Table 1).

Among all GC users, concurrent antibiotics (59.1%), respiratory/otologic drugs (50.1%), or both (31.8%) were frequently reimbursed at the index date, suggesting that underlying ENT (ear nose throat) and upper respiratory tract infections were often present (Table 1).

Table 1. Characteristics of oral glucocorticoid (GC) initiators, overall and according to number of oral GC reimbursements over year following treatment initiation

	All GC initiators	No. of GC reimbursements over year following treatment initiation		
		1	2 to 5	≥6
	N=206,759	N=139,703	N=63,267	N=3,789
Males	86,861 (42.0)	60,460 (43.3)	24,717 (39.1)	1,684 (44.4)
Age groups (years)				
18-49	121,589 (58.8)	83,828 (60.0)	36,794 (58.2)	967 (25.5)
50-59	34,245 (16.6)	22,697 (16.3)	10,908 (17.2)	640 (16.9)
60-69	24,703 (12.0)	16,223 (11.6)	7,764 (12.3)	716 (18.9)
70-79	16,048 (7.8)	10,316 (7.4)	4,898 (7.7)	834 (22.0)
≥80	10,174 (4.9)	6,639 (4.8)	2,903 (4.6)	632 (16.7)
Comorbidities at risk for GC users[a]	21,830 (10.6)	14,020 (10.0)	6,883 (10.9)	927 (24.5)
Diabetes	10,906 (5.3)	7,229 (5.2)	3,218 (5.1)	459 (12.1)
Psychotic disorders	5,418 (2.6)	3,465 (2.5)	1,816 (2.9)	137 (3.6)
Osteoporosis	6,822 (3.3)	4,155 (3.0)	2,249 (3.6)	418 (11.0)
Identified GC recognized indications[a]	56,518 (27.3)	33,087 (23.7)	21,116 (33.4)	2,315 (61.1)
Obstructive pulmonary diseases	44,116 (21.3)	26,662 (19.1)	16,462 (26.0)	992 (26.2)
Cancer	13,256 (6.4)	6,864 (4.9)	5,182 (8.2)	1,210 (31.9)
Rheumatic diseases	1,988 (1.0)	848 (0.6)	682 (1.1)	458 (12.1)
Rheumatoid arthritis	809 (0.4)	312 (0.2)	283 (0.5)	214 (5.7)
Polymyalgia rheumatica/giant cell arteritis	204 (0.1)	23 (0.0)	34 (0.1)	147 (3.9)
Inflammatory bowel diseases	1,243 (0.6)	569 (0.4)	549 (0.9)	125 (3.3)
Multiple sclerosis	429 (0.2)	274 (0.2)	148 (0.2)	7 (0.2)
Concurrent drugs at index date				
Antibiotics	122,107 (59.1)	84,697 (60.6)	36,504 (57.7)	906 (23.9)
Respiratory/otological drugs[b]	103,555 (50.1)	71,327 (51.1)	31,597 (49.9)	631 (16.7)
Concurrent antibiotics and respiratory/otological drugs	65,796 (31.8)	45,076 (32.3)	20,383 (32.2)	337 (8.9)
Anti-inflammatory	13,507 (6.5)	8,902 (6.4)	4,332 (6.9)	273 (7.2)
Analgesics	95,148 (46.0)	64,974 (46.5)	28,862 (45.6)	1,312 (34.6)

[a] At least one; [b] Nasal and throat preparations, antihistamines for systemic use, cough and cold preparations, otological drugs.

Therapeutic behaviour associated with prescription of GCs

Among GC initiators, 1,469 (0.7%) individuals were considered at increased risk of GC-induced osteoporosis related to long-term treatment (≥6 reimbursements/year) and to age (≥70 years) or to a past history of non-treated osteoporosis. Among them, 61.5% had at least one measure aiming at preventing/monitoring osteoporosis over the year following treatment initiation: DXA was performed in 189 (12.9%) individuals and 891 (60.6%) individuals were reimbursed at least one drug for osteoporosis management. Nearly 55% of at-risk individuals received calcium and/or vitamin D, 27.4% a bisphosphonate and 5.0% another drug for osteoporosis prevention (Table 2).

Table 2. Measures for prevention/monitoring of osteoporosis among individuals at increased risk. Figures are numbers (percentages) of individuals

	Individuals at increased risk[a] N=1,469
At least one measure during the year following treatment initiation	903 (61.5)
DXA	189 (12.9)
Drugs for osteoporosis management	890 (60.6)
Vitamin D ± Calcium	796 (54.2)
Biphosphonates	402 (27.4)
Biphosphonates	305 (20.8)
Fixed association of biphosphonates and vitamin D ± calcium	133 (9.1)
Other drugs for osteoporosis management	73 (5.0)
Calcitonin	10 (0.7)
Denosumab	5 (0.3)
Raloxifene	9 (0.6)
Strontium ranelate	46 (3.1)
Teriparatide	9 (0.6)

[a]At least 6 reimbursements of oral glucocorticoids per year and (i) age ≥70 years or (ii) past history of untreated osteoporosis
DXA: Dual-energy X-ray Absorptiometry

Over the year following treatment initiation, 10.8% of GC initiators had at least one concurrent reimbursement of oral GC and PPI without known concurrent NSAID or aspirin use; this concerned nearly half (49.8%) of long-term users *versus* 7.1% of short-term users. Concurrent reimbursement of oral GCs and potassium supplementation concerned 23.7% of long-term users of whom 37.3% never had any serum potassium assay during the two weeks preceding the prescription. Conversely, concurrent use of oral GCs and potassium supplementation was infrequent among individuals who had <6 reimbursements of GCs over the year following treatment initiation (<2%).

DISCUSSION

Statement of principal findings

This population-based study provides a representative description of oral GC use in adults and its trends over the past seven years in France. The annual prevalence of GC use in the general population, which was already high in 2007, increased by 14%, i.e. about 2% per year. In 2014, 17% of the French adult population had at least one reimbursement of an oral GC. The most prevalent use was observed in individuals aged 50 to 59 and the highest increase was in women aged 50-69. The overwhelming majority (68%) of new GC use was short-term (unique reimbursement) and apparently related to ENT and upper respiratory tract infections. Overall, 1.8% of GC initiators were considered as chronic users. Of note, comorbidities likely to be worsened by GC use (diabetes, psychotic disorders, osteoporosis) were found at treatment initiation among nearly one-quarter of chronic users.

Therapeutic measures for the prevention of GC-induced osteoporosis appeared to be insufficiently prescribed among individuals judged at increased risk. Conversely, the concurrent prescription of PPIs and potassium supplementation was found to be frequent, in particular in chronic users, although the toxicity of GCs for the upper gastrointestinal tract and the risk of hypokalaemia is questionable or, at least, debated.

Strengths and weaknesses of study

The major strength of the study is use of the EGB database, which is fully representative of the whole French population. This ensures the generalizability of the results to a national level. Indeed, a unique healthcare insurance system guarantees universal coverage for all French residents, independently of their socio-economic status. The study also suffers from some limitations that are shared by almost all studies conducted on reimbursement claims databases. First, the database did not provide direct information about medical indication for each reimbursement, so we used data from diagnoses related to hospital stays or chronic diseases and concurrent drugs as proxies of the illness they were likely to be used for. Nonetheless, full reimbursement of healthcare for chronic diseases in France is subject to prior approval by the national health insurance system on the basis of an official form duly signed by the prescriber certifying that the patient's condition requires full coverage. This strengthens the validity of the diagnosis considered for these diseases. Secondly, given that the database does not provide the total duration of treatments, short- *versus* long-term use was defined according to the number of reimbursements per year. While a dispensing, when unique, is the most robust indicator of short-term use, it was rational for long-term use to postulate that individuals with at least six reimbursements per year were chronic users, even if renewals were not consecutive.

Strengths and weaknesses in relation to other studies

The use of oral GCs in the general population has received little attention until now.[17-21] Contrary to the present study, none of the previous studies were truly representative of the general source population, and the results from studies conducted on the UK medical databases [17, 20] seem to be the most comparable to ours. However, direct comparisons are hampered by methodological differences as those studies focused on long-term users and assessed prevalence rates by considering

person-time of follow-up rather than one-year prevalence estimates, as in the present study. They found a prevalence estimate of about 1% at any moment,[17, 20] a 34% increase in their use being reported between 1989 and 2008.[17] Our results regarding the proportion of prevalent users with at least six reimbursements per year (0.7% in 2014) are consistent with previous studies on chronic use. Consequently, another cornerstone of our study is that it estimated the overall prevalence of GC use. This highlighted a particularly high use of short-term GC therapy (unique reimbursement, 68%) that could be specific to France. Regarding the 14% increase observed in the prevalent use of oral GCs, it is unlikely to be explained only by the expected increase in the annual incidence of their recognized indications in the general population of adults. Moreover, results obtained over a 20-year period in the UK showed that patients newly diagnosed with rheumatoid arthritis or inflammatory bowel diseases are less likely to receive long-term oral GC prescriptions today.[17] Thus, the increase in prevalent use could mainly be due to more and more prescribing in unjustified situations.

Possible explanations and implications for clinicians and policymakers

As mentioned above, 68% of GC initiators received a unique GC reimbursement, most of them being aged less than 50 years. Concurrent use of antibiotics and drugs for respiratory/otological disorders were frequently found at treatment initiation in these individuals, suggesting the presence of underlying ENT or upper respiratory tract infections. Oral GCs are relatively safe for short-term therapy. On the other hand, infections, neuropsychiatric disorders and worsening of pre-existent diabetes are known complications of GC therapy, even in those exposed only for a few days or weeks. The frequent pattern of use found in this study questions the rationale of prescribing oral GCs in adults. For example, as recently emphasized in a systematic review on adult chronic sinusitis management,[22] first-line therapy consists of daily saline irrigation with topical GC therapy. In this indication, a short course of systemic GC (1-3 weeks) should be considered only in the event of persistent symptoms or acute exacerbation, especially in patients with nasal polyps.

Also worrying was the high prevalence found for comorbidities predisposing to adverse reactions with oral GCs at treatment initiation in long-term users (25%). As long-term users were older, a high prevalence of diabetes was expected. Nevertheless, this frequent comorbidity requires attention given the available data showing that diabetes monitoring in long-term GC users is very

insufficient [23]. Adverse psychiatric reactions with GCs are also well known [24] and include a wide range of manifestations including affective disorders and psychotic reactions. Uncontrolled psychotic disorders are a contraindication for GC therapy and the 3.6% prevalence of psychotic disorders at oral GC initiation found in long-term users is of concern. Moreover, few data are available for identifying patients at increased risk of such neuropsychiatric disorders. Risk may be higher in patients with a past history of neuropsychiatric disorders or with exposure to high doses although dose levels are not predictive of the onset, type or severity of reactions.[25] In this respect, short- and mid-term users (who represented 98% of the cohort) are also at risk.

Another key result is the apparently inappropriate prescribing of therapeutic measures associated with GC therapy. The latter is a recognized cause of osteoporosis and osteoporosis management and DXA measurement should be systematically undertaken in patients whose GC therapy is expected to exceed three consecutive months, especially those at high risk for fractures including patients aged 70 years and over.[2] In this study, the use of any drug for osteoporosis management was recorded for fewer than two-thirds of patients at increased risk; in particular only 27% were prescribed a biphosphonate. DXA measurement was performed in 13%. This is consistent with previous reports that drugs for osteoporosis management and DXA measurement are used in only a minority of patients exposed to long-term GC therapy.[16, 18, 19] Conversely, half of the long-term GC users had concurrent reimbursement of PPIs, apparently without any NSAID or aspirin use, although no consensual recommendation exists regarding the need for such gastric protection. Except in the event of concomitant NSAID use in elderly people, PPIs are advised only if patients have risk factors for peptic ulcer, such as an inflammatory disease.[5, 26, 27] Moreover, inappropriate concurrent use of PPIs in long-term GC users is particularly concerning given that fractures and infection are also associated with PPI use.[28] Some practitioners prescribe potassium supplementation while others do not.[8] The present findings suggest that this is infrequent in France except in long-term users (24%). The latter were more likely to be adequately monitored than short- and mid-term users, two-thirds having kalaemia monitoring at least once, which is in line with a previous report.[23]

Unanswered questions and future research

In conclusion, oral GC use is very widespread among adults in France and its prevalence steadily increased over the 2007-2014 period, the overwhelming majority of this being short-term. This could mainly be due to the growing number of unjustified prescriptions rather than to situations with a favourable benefit/risk ratio. This hypothesis needs to be confirmed by further research and the impact of this extensive use in the population should be estimated. Moreover, our findings plead for the development of interventions designed to improve the monitoring of chronic users with regard to the frequent comorbidities at risk and inappropriate prescribing of preventive therapeutic measures.

Contributors: ABL, AP, LF, BB, PN conceptualized and designed the work. EP collected the data and carried out the analysis. ABL, AP, LF, BB, PN interpreted the data. ABL wrote the first draft, and all the authors critically revised and approved the final manuscript.

Funding: The present study is part of the Drugs Systematized Assessment in real-liFe Environment (DRUGS-SAFE) research program funded by the French Medicines Agency (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*, ANSM; grants received for the year 2016: 950,000 euros). This program aims at providing an integrated system allowing the concomitant monitoring of drug use and safety in France. The potential impact of drugs, frailty of populations and seriousness of risks drive the research program.

This publication represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

Competing interest: None.

Ethics approval: In accordance with French regulations, ethics committee approval was not required for this observational study conducted on anonymous medico-administrative data.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Figure 1. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014. Prevalence estimates with 95% CIs (error bars) A) overall and by sex, B) by age

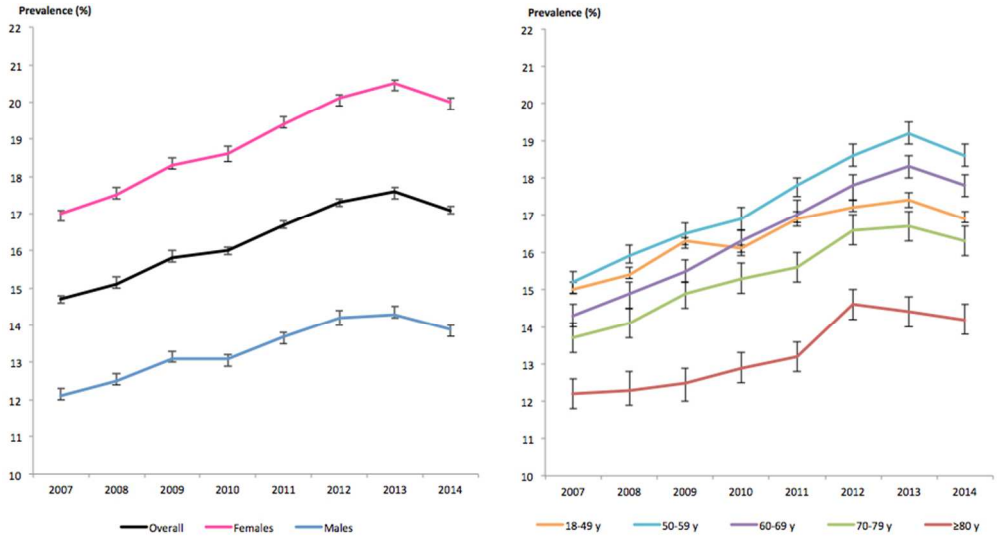

Figure 1. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014. Prevalence estimates with 95% CIs (error bars) A) overall and by sex, B) by age

335x179mm (72 x 72 DPI)

Supplementary file

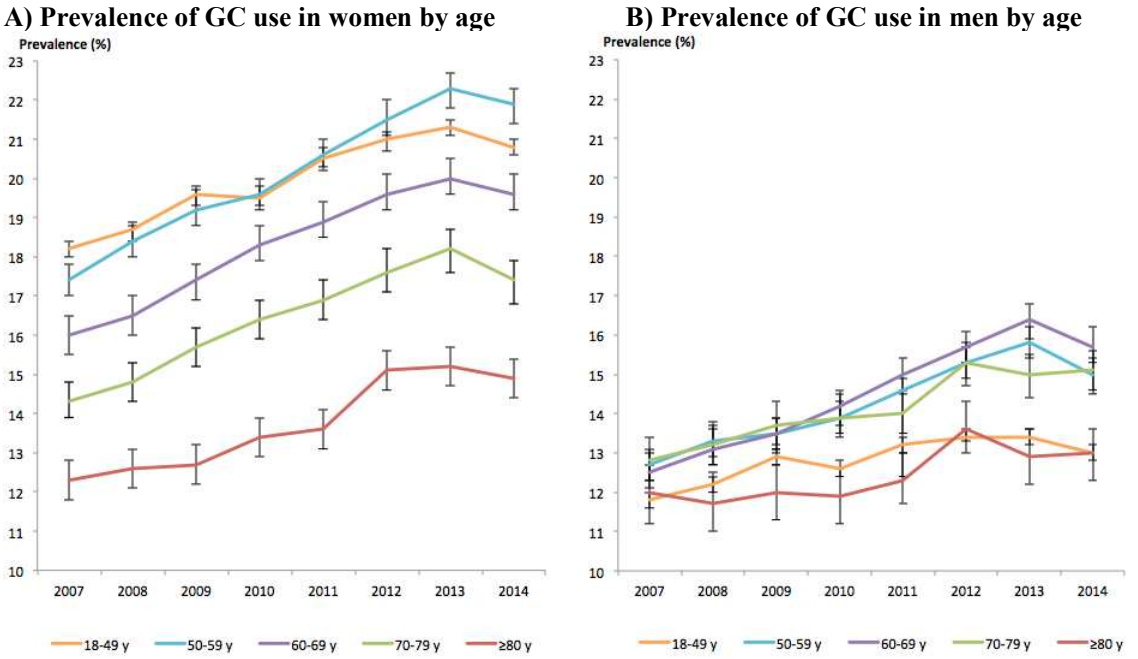

Figure S1. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014, in women (A) and men (B) according to age. Prevalence estimates with 95% CIs (error bars)

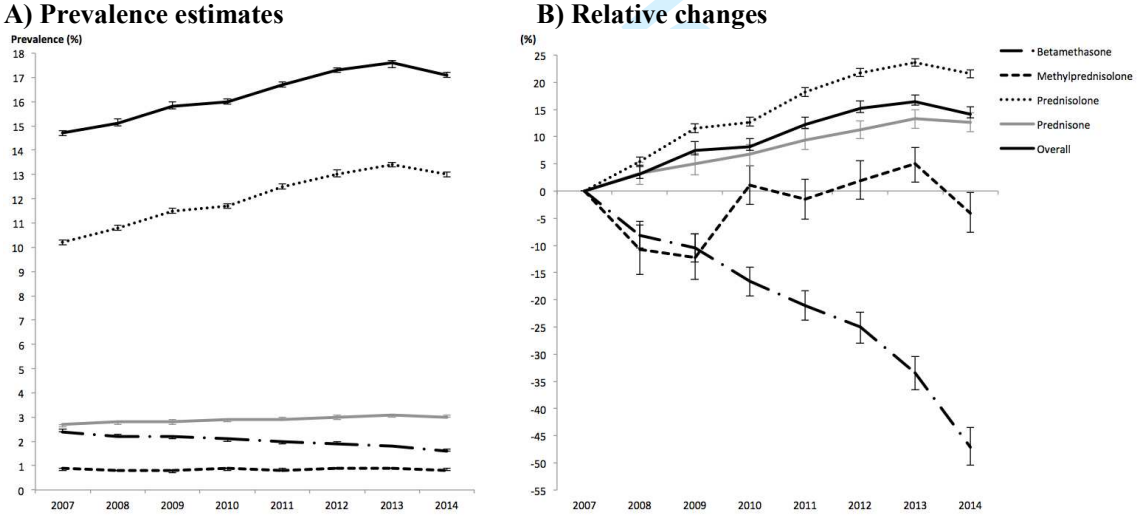

Figure S2. Trends in prevalence of oral glucocorticoid use in France per year from 2007 to 2014 by products. A) Prevalence estimates with 95%CI (error bars) and B) relative changes in reference to year 2007

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any pre-specified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#4 to 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	#5 to 6 Not applicable (NA) #5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5 to 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5 to 6
Bias	9	Describe any efforts to address potential sources of bias	#5
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#7
		(*b*) Describe any methods used to examine subgroups and interactions	#7
		(*c*) Explain how missing data were addressed	#7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7 #8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Data available on request
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	#9 to 10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	#7 to 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	#8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	#10 to 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#12 to 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	#11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015905.R1
Article Type:	Research
Date Submitted by the Author:	27-Mar-2017
Complete List of Authors:	Bénard-Laribière, Anne; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219 Pariente, Antoine; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale Pambrun, Elodie; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219 Bégaud, Bernard; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale Fardet, Laurence; EA 7379, Université Paris Est Créteil (UPEC), CHU Henri Mondor, Service de Dermatologie Noize, Pernelle; Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, CHU Bordeaux, Service de Pharmacologie Médicale, CIC Bordeaux CIC1401
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	glucocorticoids, pharmacoepidemiology, drug utilization, insurance health reimbursement

Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France

Anne Bénard-Laribière[1], Antoine Pariente[1,2], Elodie Pambrun[1], Bernard Bégaud[1,2], Laurence Fardet[4,5], Pernelle Noize[1,2,3]

Affiliations:

[1]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team PHARMACOEPIDEMIOLOGY, UMR 1219, F-33000 Bordeaux, France

[2]CHU Bordeaux, Service de Pharmacologie Médicale, F-33000 Bordeaux, France

[3]CIC Bordeaux CIC1401, F-33000 Bordeaux, France

[4]EA 7379, Université Paris Est Créteil (UPEC), F-94000 Créteil, France

[5]CHU Henri Mondor, Service de Dermatologie, F-94000 Créteil, France

Correspondence to: Anne Bénard-Laribière, Service de Pharmacologie Médicale, Hôpital Pellegrin, CHU, F-33076 Bordeaux cedex, France, anne.benard@u-bordeaux.fr, Phone +33 557571560, Fax +33 557574671

Word count: 3,148

ABSTRACT

Objectives: To study trends in use of oral glucocorticoids (GCs) among adults, characteristics of oral GC initiators and prescriptions for the prevention of potential adverse effects associated with GC therapy.

Design: First, a cross-sectional study repeated yearly was performed from 2007 to 2014 in a nationwide representative sample. Second, characteristics of initiators and patterns of GC therapy during the year following treatment initiation were described in a cohort of patients who began GC between 2007 and 2013.

Setting: Population-based study using data from the French reimbursement healthcare system (covering approximately 90% of the population) in patients aged ≥18 years.

Results: Over the study period, the prevalence of oral GC use ranged from 14.7% to 17.1% [17.0-17.2%] with a significant increase of 14.1% [+13.5 to +14.8%]. The 2007-2013 cohort of oral GC initiators comprised 206,759 individuals. Oral GC use was mostly short-term (68% of unique reimbursement) and more than half of short-term users took concurrent antibiotics or respiratory/otologic drugs. Chronic users (≥6 reimbursements/year) represented 1.8% (n=3,789) of the cohort. The proportion of chronic users with comorbidities likely to be worsened by GC use (diabetes, psychotic disorders, osteoporosis) was 25%. Among patients at increased risk of osteoporosis, 62% received specific prevention/monitoring measures and only 27% had a biphosphonate. Half of chronic oral GC users had a concurrent reimbursement of a proton pump inhibitor in the absence of NSAID use.

Conclusions: Oral GC use was highly widespread and increased among adults from 2007 to 2014. The overwhelming short-term use could mainly concern a growing use of unjustified prescriptions rather than situations with a favourable benefit/risk ratio. For chronic users, our findings plead for the development of interventions designed to improve monitoring with regard to the frequent comorbidities at risk and inappropriate prescribing of preventive therapeutic measures.

Strengths and limitations of this study

- The main strength is that it is representative of the general population owing to the data source, a healthcare insurance database with exhaustive recording of reimbursements and hospitalizations.
- A limitation is that the database does not include direct information on medical indications, which could be derived from data on chronic diseases, hospitalizations and concurrent drugs.
- Altogether, this population-based study provides a description of oral glucocorticoid (GC) use and trends in adults over an 8-year period from 2007 to 2014.

INTRODUCTION

Oral glucocorticoids (GCs) have been used for more than 60 years for their substantial anti-inflammatory and immunosuppressive effects in several acute and chronic disorders, both for reducing disease activity and pain.[1] However, their use is limited by the occurrence of adverse reactions related to their pharmacological properties that are mainly to be feared with higher dosages or long-term use. These associated risks include infections, osteoporosis and fractures, hyperglycaemia, neuropsychiatric disorders and muscle atrophy. Recommendations on the management of GC therapy based on expert consensus are available for the prevention of GC-induced osteoporosis;[2-4] regarding other significant adverse reactions, advice on pre-treatment and treatment monitoring have been issued [5, 6] but no consensual recommendations exist.

Besides these well-known adverse consequences, the relevance of some other potential adverse reactions is debated such as the impact on electrolyte homeostasis due to mineralocorticoid effects or the risk of peptic ulcer. While potassium loss seems negligible in practice,[7] some physicians persist in prescribing potassium supplementation which, in some situations, may carry a risk of marked hyperkalaemia.[8] Similarly, despite the literature suggesting no benefit from proton pump inhibitors (PPIs) prophylaxis in patients taking systemic GCs without concomitant non-steroidal anti-inflammatory (NSAID) use,[9, 10] many prescribers still consider GCs as a cause of upper-gastrointestinal complications and systematically add PPIs to their prescriptions.[11]

Few studies have reported the use of oral GCs in the general population, and short-term use has rarely been quantified as it is considered safe. This population-based study aimed at describing trends in the use of oral GCs among adults, the characteristics of GC initiators and the prescriptions for the prevention of potential adverse effects associated with GC therapy.

METHODS

Data source

The study was conducted using the French reimbursement database (*Echantillon Généraliste de Bénéficiaires*, EGB). The EGB is a representative sample of the population covered by the national healthcare insurance system (approximately 90% of the whole population, irrespective of socio-

economic status) obtained by 1/97th random sampling with stratification on sex and age. For all beneficiaries, it consists of the exhaustive recording of drug reimbursements, with identification of medication packs, including the number and dosage strengths of treatment units. The database also contains hospitalization data (diagnoses and dates), and the existence of certain chronic diseases (*Affections de Longue Durée*, ALD, an administrative status allowing full reimbursement of health care for a given condition; *e.g.* diabetes, cancer, psychosis). Diagnoses or indications for prescribing are not collected in the EGB database, nor the dose prescribed or the duration of treatment. Details on the EGB database have been described elsewhere.[12, 13]

Study design

Cross-sectional study

In order to study temporal trends in the use of GCs, a cross-sectional study was repeated yearly among the population aged ≥18 years, from January 1st 2007 to December 31st 2014. All individuals who had at least one reimbursement of an oral GC (i.e., betamethasone, dexamethasone, methylprednisolone, prednisolone, and prednisone) were identified for each year studied.

Cohort study

To study characteristics of GC users and therapeutic behaviour associated with the prescription, a cohort of oral GC initiators was identified. GC initiators were defined as an incident reimbursement of oral GC between January 1st 2007 and 31st December 2013, without any in the preceding year. This definition was retained to ensure incident use was identified in a conservative manner even if other definitions can be found in the literature (e.g. prescription-free, 90-day [14] or 6-month period [15, 16]). The index date was the date the incident GC was reimbursed. Each GC initiator was followed until one year since index date, the date of death, or the end of data availability in the database, whichever came first. Identified individuals could only contribute once to the cohort constitution.

Characteristics of GC initiators: GC initiators were described in terms of age and sex at index date. Comorbidities which may represent situations at risk in the event of GC use (*i.e.* diabetes, psychotic disorders, and osteoporosis) were described, as were chronic disorders constituting recognized indications for GC therapy: rheumatic diseases (e.g. rheumatoid arthritis, polymyalgia rheumatica/giant cell arteritis, lupus and vasculitis), obstructive pulmonary diseases (*i.e.* asthma, chronic obstructive pulmonary disease, and chronic respiratory failure), inflammatory bowel diseases (*i.e.* Crohn's disease and ulcerative colitis) and multiple sclerosis. Comorbidities and indications for oral GC treatment were identified using data from diagnoses related to hospital stays or chronic diseases (ALDs), and medication reimbursement data in the 12-month period preceding the patient's index date. A description of drugs reimbursed at index date (concurrent drugs) was also performed as these potentially reflect the indication of GC therapy.

Therapeutic behaviour associated with the prescription of GCs: Over the year following GC treatment initiation, we scrutinized two types of preventive measures: (i) those that should be systematically considered such as prevention/monitoring of osteoporosis among individuals at increased risk of osteoporosis; and (ii) those for whom no consensus exists and/or that might be inappropriate (potassium supplementation without serum potassium assay, and proton pump inhibitors (PPI) prophylaxis without concurrent NSAID or aspirin use).

To assess the prevention and monitoring of osteoporosis, individuals at increased risk of GC-induced osteoporosis were defined as those who had at least six reimbursements of GCs during the 12-month period following the index date and: (i) were aged 70 years and over, or (ii) had a past history of untreated osteoporosis during the 12 months preceding the index date. Measures for prevention/monitoring of osteoporosis among these individuals were identified by at least one of the following criteria: (i) bone mineral density measurement (at least one reimbursement for dual-energy X-ray absorptiometry, DXA), or (ii) prescription of drugs indicated for osteoporosis management (at least one reimbursement for calcium, vitamin D, bisphosphonates, denosumab, raloxifene, teriparatide, strontium ranelate, calcitonin).

For non-consensually recommended measures, potentially inappropriate potassium supplementation was defined as at least one concurrent reimbursement of oral GC and potassium supplements without any serum potassium assay during the two preceding weeks. *A priori* non-indicated prescription of PPIs was defined as at least one concurrent reimbursement of oral GC and PPI in the absence of NSAID or aspirin at the same date.

Data analysis

Trends in use of oral GCs

The annual prevalence of GC use was defined as the proportion of GC users per 100 individuals for the corresponding year. It was first calculated for GCs overall and then by considering each GC individually. All prevalence estimates were further stratified according to the number of GCs reimbursed per year (1, 2 to 5, ≥6), and by sex and age (five categories according to age on January 1st in each year: 18-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years), and were quantified together with their 95% two-sided confidence intervals (95%CIs). To study trends in prevalent use over the study period, relative changes in prevalence of use were estimated by using the year 2007 as reference. Relative change estimates, quantified together with their two-sided 95%CI, were calculated using the percentiles bootstrap method.

Characteristics of GC initiators and therapeutic behaviour associated with prescription of GCs

All parameters were examined overall and stratified according to the duration of therapy. The EGB database does not provide the total duration of treatments but GC treatment is issued for a maximum of 30 days in France and individuals have to renew their treatment each month. We consequently assessed GC treatment duration according to the number of oral GC reimbursements (consecutive or not) identified during the 12-month period following the index date. Users who had a unique reimbursement were arbitrarily defined as *short-term users*, those who had 2 to 5 reimbursements as *mid-term users*, and those with ≥6 reimbursements as *long-term users*. We assumed that individuals with ≥6 reimbursements/year were treated for chronic diseases. Measures for

the prevention of osteoporosis were examined only for individuals with an increased risk of osteoporosis as defined above.

All analyses were performed using SAS® software (SAS Institute, version 9.4, North Carolina, USA). All codes used for the identification of the studied comorbidities and medications are listed in Supplementary files (Tables S1 to S5).

RESULTS

Trends in use of oral GCs from 2007 to 2014

Of the 382,572 individuals included in the study in 2007, 56,126 had at least one reimbursement of an oral GC: the prevalence of GC use was 14.7% [95%CI: 14.6-14.8%] in 2007. It was 17.1% [17.0-17.2%] in 2014, corresponding to a 14.1% increase [+13.5 to +14.8%] compared to 2007 (Figure 1). This rise was more pronounced in individuals aged 50-59 years (+18.4% [+17.0 to +20.0%]) and 60-69 years (+19.7% [+17.9 to +21.5%]). It mostly concerned prednisolone (+21.6% [+20.8 to +22.3%]) (online Figure S1); this was the most used GC over the study period, irrespective of age and sex. The prevalence of use was higher among women whatever their age, the highest value being observed in those aged 50-59 years (21.9% in 2014 [21.4 to 22.3%]) (online Figure S2). Concerning the number of GCs reimbursed per year, the prevalence of unique reimbursement slightly increased from 10.3% in 2007 to 11.8% in 2014 (+12.7% [+11.8 to +13.5%]). The proportion of individuals who had 2 to 5 reimbursements per year rose from 3.8% to 4.6% (+18.6% [+17.4 to +19.9%]). Conversely, the percentage of individuals with ≥6 reimbursements per year remained stable and ranged between 0.6% and 0.7% (+7.9% increase [+3.8 to +11.8%] compared to 2007).

Characteristics of GC initiators

The 2007-2013 cohort of GC initiators comprised 206,759 individuals; 58.0% were women and median age was 45 years (interquartile range, IQR: 32-59). More than two thirds of initiators (67.6%) had a unique reimbursement of GC over the year following treatment initiation (short-term users). Mid-term users represented 30.6% of the study cohort and long-term users 1.8%. Compared with short- and mid-term users, long-term users were more likely to be older (median age 63 years,

IQR: 49-76); one quarter (24.5%) had at least one comorbidity at treatment initiation that was likely to increase the risk of adverse drug reaction in the event of GC use (diabetes: 12.1%; osteoporosis: 11.0%; psychotic disorders: 3.6%). Recognized GC indications were identified in 61.1% of long-term users. Among these potential indications, obstructive pulmonary diseases (26.2%), rheumatic diseases (12.1%) and inflammatory bowel diseases (3.3%) were the most frequent, and nearly 32% of these individuals had a cancer (Table 1).

Among all GC users, concurrent antibiotics (59.1%), respiratory/otologic drugs (50.1%), or both (31.8%) were frequently reimbursed at the index date, suggesting that underlying ENT (ear nose throat) and upper respiratory tract infections were often present (Table 1).

Table 1. Characteristics of oral glucocorticoid (GC) initiators, overall and according to number of oral GC reimbursements over year following treatment initiation (figures are percentages)

	All GC initiators N=206,759	Short-term users* N=139,703	Mid-term users* N=63,267	Long-term users* N=3,789
Males	42.0	43.3	39.1	44.4
Age groups (years)				
18-49	58.8	60.0	58.2	25.5
50-59	16.6	16.3	17.2	16.9
60-69	12.0	11.6	12.3	18.9
70-79	7.8	7.4	7.7	22.0
≥80	4.9	4.8	4.6	16.7
Mean number of reimbursements/year (±SD)	1.6 (±1.4)	1*	2.5 (±0.8)	9.2 (±3.1)
Comorbidities at risk for GC users[a]	10.6	10.0	10.9	24.5
Diabetes	5.3	5.2	5.1	12.1
Psychotic disorders	2.6	2.5	2.9	3.6
Osteoporosis	3.3	3.0	3.6	11.0
Identified GC recognized indications[a]	27.3	23.7	33.4	61.1
Obstructive pulmonary diseases	21.3	19.1	26.0	26.2
Cancer	6.4	4.9	8.2	31.9
Rheumatic diseases	1.0	0.6	1.1	12.1
Rheumatoid arthritis	0.4	0.2	0.5	5.7
Polymyalgia rheumatica/giant cell arteritis	0.1	0.0	0.1	3.9
Inflammatory bowel diseases	0.6	0.4	0.9	3.3
Multiple sclerosis	0.2	0.2	0.2	0.2
Concurrent drugs at index date				
Antibiotics	59.1	60.6	57.7	23.9
Respiratory/otological drugs[b]	50.1	51.1	49.9	16.7
Concurrent antibiotics and respiratory/otological drugs	31.8	32.3	32.2	8.9
Anti-inflammatory	6.5	6.4	6.9	7.2
Analgesics	46.0	46.5	45.6	34.6

*Short-term users: 1 reimbursement/year; mid-term users: 2 to 5 reimbursements/year; long-term users: ≥6 reimbursements
[a] At least one; [b] Nasal and throat preparations, antihistamines for systemic use, cough and cold preparations, otological drugs

Therapeutic behaviour associated with prescription of GCs

Among GC initiators, 1,469 (0.7%) individuals were considered at increased risk of GC-induced osteoporosis related to long-term treatment (≥6 reimbursements/year) and to age (≥70 years) or to a past history of non-treated osteoporosis. Among them, 61.5% had at least one measure aiming at preventing/monitoring osteoporosis over the year following treatment initiation: DXA was performed in 189 (12.9%) individuals and 891 (60.6%) individuals were reimbursed at least one drug for osteoporosis management. Nearly 55% of at-risk individuals received calcium and/or vitamin D, 27.4% a bisphosphonate and 5.0% another drug for osteoporosis prevention (Table 2).

Table 2. Measures for prevention/monitoring of osteoporosis among individuals at increased risk (figures are percentages)

	Individuals at increased risk[a] N=1,469
At least one measure during the year following treatment initiation	61.5
DXA	12.9
Drugs for osteoporosis management	60.6
Vitamin D ± Calcium	54.2
Biphosphonates	27.4
Biphosphonates	20.8
Fixed association of biphosphonates and vitamin D ± calcium	9.1
Other drugs for osteoporosis management	5.0
Calcitonin	0.7
Denosumab	0.3
Raloxifene	0.6
Strontium ranelate	3.1
Teriparatide	0.6

[a]At least 6 reimbursements of oral glucocorticoids per year and (i) age ≥70 years or (ii) past history of untreated osteoporosis
DXA: Dual-energy X-ray Absorptiometry

Over the year following treatment initiation, 10.8% of GC initiators had at least one concurrent reimbursement of oral GC and PPI without known concurrent NSAID or aspirin use; this concerned nearly half (49.8%) of long-term users *versus* 7.1% of short-term users. Concurrent reimbursement of oral GCs and potassium supplementation concerned 23.7% of long-term users of whom 37.3% never had any serum potassium assay during the two weeks preceding the prescription. Conversely, concurrent use of oral GCs and potassium supplementation was infrequent among individuals who had <6 reimbursements of GCs over the year following treatment initiation (<2%) (Table 3).

Table 3. Measures for kalaemia and gastric protection associated with the prescription of oral glucocorticoids (GC) therapy over the year following treatment start (figures are percentages)

	All GC initiators N=206,759	Short-term users* N=139,703	Mid-term users* N=63,267	Long-term users* N=3,789
At least one concurrent reimbursement of GC and potassium supplements	1.3	0.5	1.8	23.7
Without any serum potassium level measurement during the preceding 2-week period	0.8	0.4	1.3	8.8
At least one concurrent reimbursement of GC and PPI without concurrent NSAID or aspirin use	10.8	7.1	16.7	49.8

*Short-term users: 1 reimbursement/year; mid-term users: 2 to 5 reimbursements/year; long-term users: ≥6 reimbursements
NSAID: Non Steroidal Anti-Inflammatory Drug; PPI: Proton Pump Inhibitor

DISCUSSION

Statement of principal findings

This population-based study provides a representative description of oral GC use in adults and its trends over the past seven years in France. The annual prevalence of GC use in the general population, which was already high in 2007, increased by 14%, i.e. about 2% per year. In 2014, 17% of the French adult population had at least one reimbursement of an oral GC. The overwhelming majority (68%) of new GC use was short-term (unique reimbursement) and apparently related to ENT and upper respiratory tract infections. Overall, 1.8% of GC initiators were considered as chronic users. Of note, comorbidities likely to be worsened by GC use (diabetes, psychotic disorders, osteoporosis) were found at treatment initiation among nearly one-quarter of chronic users. Therapeutic measures for the prevention of GC-induced osteoporosis appeared to be insufficiently prescribed among individuals judged at increased risk. Conversely, the concurrent prescription of PPIs and potassium supplementation was found to be frequent, in particular in chronic users, although the toxicity of GCs for the upper gastrointestinal tract and the risk of hypokalaemia is questionable or, at least, debated.

Strengths and weaknesses of study

The major strength of the study stands in the use of the EGB database, fully representative of the whole French population, which ensures the generalizability of the results to a national level. This use however implies some limitations inherent to almost all studies conducted on reimbursement claims databases. First, the database does not provide direct information about medical indication for each reimbursement, so we used data from diagnoses related to hospital stays or chronic diseases and

concurrent drugs as proxies of potential GC indications. Secondly, given that the database does not provide the prescribed duration of treatments, this was defined according to the number of reimbursements per year. If a unique dispensing appears as an indisputable indicator of short-term use, we postulated that individuals with at least six reimbursements per year were chronic users even if renewals were not consecutive, which can be discussed.

Strengths and weaknesses in relation to other studies

The use of oral GCs in the general population has received little attention until now.[17-21] Contrary to the present study, none of the previous studies were truly representative of the general source population, and the results from studies conducted on the UK medical databases [17, 20] seem to be the most comparable to ours. However, direct comparisons are hampered by methodological differences as those studies focused on long-term users. They found a prevalence estimate of about 1% at any moment,[17, 20] a 34% increase in their use being reported between 1989 and 2008.[17] Our results regarding the proportion of prevalent users with at least six reimbursements per year (0.7% in 2014) are consistent with previous studies on chronic use. Consequently, another cornerstone of our study is that it estimated the overall prevalence of GC use. This highlighted a particularly high use of short-term GC therapy (unique reimbursement, 68%) that could be specific to France. Regarding the 14% increase observed in the prevalent use of oral GCs, it is unlikely to be explained only by the expected increase in the annual incidence of their recognized indications in the general population of adults. Moreover, results obtained over a 20-year period in the UK showed that patients newly diagnosed with rheumatoid arthritis or inflammatory bowel diseases are less likely to receive long-term oral GC prescriptions today.[17]

Possible explanations and implications for clinicians and policymakers

As mentioned above, 68% of GC initiators received a unique GC reimbursement, most of them being aged less than 50 years. Concurrent use of antibiotics and drugs for respiratory/otological disorders were frequently found at treatment initiation in these individuals, suggesting the presence of underlying ENT or upper respiratory tract infections. Oral GCs are relatively safe for short-term therapy. On the other hand, infections, neuropsychiatric disorders and worsening of pre-existent

diabetes are known complications of GC therapy, even in those exposed only for a few days or weeks. The frequent pattern of use found in this study questions the rationale of prescribing oral GCs in adults. For example, first-line therapy for adult chronic sinusitis consists of daily saline irrigation with topical GC therapy.[22] In this indication, a short course of systemic GC (1-3 weeks) should be considered only in the event of persistent symptoms or acute exacerbation, especially in patients with nasal polyps.

Also worrying was the high prevalence found for comorbidities predisposing to adverse reactions with oral GCs at treatment initiation in long-term users (25%). As long-term users were older, a high prevalence of diabetes was expected. Nevertheless, this frequent comorbidity requires attention given the available data showing that diabetes monitoring in long-term GC users is very insufficient.[23] Adverse psychiatric reactions with GCs are also well known.[24] Uncontrolled psychotic disorders are a contraindication for GC therapy and the 3.6% prevalence of psychotic disorders at oral GC initiation found in long-term users is of concern. Moreover, short- and mid-term users (who represented 98% of the cohort) are also at risk, as neuropsychiatric symptoms could emerge within a few days or weeks of starting the treatment.[25]

Another key result is the apparently inappropriate prescribing of therapeutic measures associated with GC therapy. The latter is a recognized cause of osteoporosis and osteoporosis management and DXA measurement should be systematically undertaken in patients whose GC therapy is expected to exceed three consecutive months, especially those at high risk for fractures including patients aged 70 years and over.[2] In this study, the use of any drug for osteoporosis management was recorded for fewer than two-thirds of patients at increased risk; in particular only 27% were prescribed a biphosphonate. DXA measurement was performed in 13%. This is consistent with previous reports that drugs for osteoporosis management and DXA measurement are used in only a minority of patients exposed to long-term GC therapy.[16, 18, 19] Conversely, half of the long-term GC users had concurrent reimbursement of PPIs, apparently without any NSAID or aspirin use, although no consensual recommendation exists regarding the need for such gastric protection. Except in the event of concomitant NSAID use in elderly people, PPIs are advised only if patients have risk factors for peptic ulcer.[5, 26, 27] Moreover, inappropriate concurrent use of PPIs in long-term GC

users is particularly concerning given that fractures and infection are also associated with PPI use.[28] Some practitioners prescribe potassium supplementation while others do not.[8] The present findings suggest that this is infrequent in France except in long-term users (24%). The latter were more likely to be adequately monitored than short- and mid-term users, two-thirds having kalaemia monitoring at least once, which is in line with a previous report.[23]

Unanswered questions and future research

In conclusion, oral GC use is very widespread among adults in France and its prevalence steadily increased over the 2007-2014 period, the overwhelming majority of this being short-term. This could partly be due to an increase in the number of unjustified prescriptions that would exceed the number of those performed in situations where the benefit/risk ratio is recognized favorable. This hypothesis needs to be confirmed by further research and the impact of this extensive use in the population should be estimated. Moreover, our findings plead for the development of interventions designed to improve the monitoring of chronic users with regard to the frequent comorbidities at risk and inappropriate prescribing of preventive therapeutic measures.

Contributors: ABL, AP, LF, BB, PN conceptualized and designed the work. EP collected the data and carried out the analysis. ABL, AP, LF, BB, PN interpreted the data. ABL wrote the first draft, and all the authors critically revised and approved the final manuscript.

Funding: The present study is part of the Drugs Systematized Assessment in real-liFe Environment (DRUGS-SAFE) research program funded by the French Medicines Agency (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*, ANSM; grants received for the year 2016: 950,000 euros). This program aims at providing an integrated system allowing the concomitant monitoring of drug use and safety in France. The potential impact of drugs, frailty of populations and seriousness of risks drive the research program.

This publication represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

Competing interest: None.

Ethics approval: In accordance with French regulations, ethics committee approval was not required for this observational study conducted on anonymous medico-administrative data.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Figure 1. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014. Prevalence estimates with 95% CIs (error bars) A) overall and by sex, B) by age

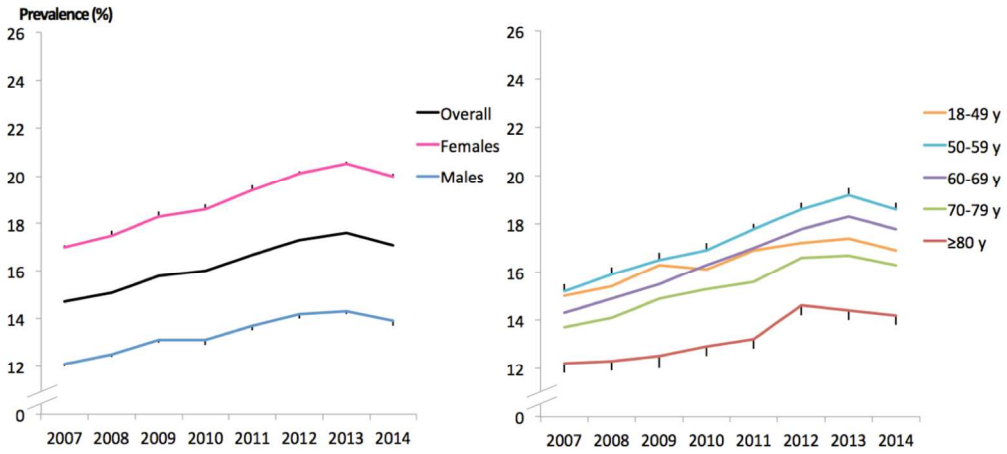


Figure 1. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014. Prevalence estimates with 95% CIs (error bars) A) overall and by sex, B) by age

159x73mm (300 x 300 DPI)

Supplementary file

Table S1. List of glucocorticoids and corresponding identification codes

Table S2. List of concurrent drugs reimbursed at index date and corresponding identification codes

Table S3. List of comorbidities at risk for glucocorticoid users and corresponding identification codes

Table S4. List of recognized indications of glucocorticoid therapy and corresponding identification codes

Table S5. List of therapeutic measures associated with the prescription of glucocorticoids and corresponding identification codes

Figure S1. Trends in prevalence of oral glucocorticoid use in France per year from 2007 to 2014 by products. A) Prevalence estimates with 95%CI (error bars) and B) relative changes in reference to year 2007

Figure S2. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014, in women (A) and men (B) according to age. Prevalence estimates with 95% CIs (error bars)

Table S1. List of glucocorticoids and corresponding identification codes

Glucocorticoids	Source	Code
Betamethasone	Drug reimbursement (ATC)	H02AB01
Dexamethasone	Drug reimbursement (ATC)	H02AB02
Methylprednisolone	Drug reimbursement (ATC)	H02AB04
Prednisolone	Drug reimbursement (ATC)	H02AB06
Prednisone	Drug reimbursement (ATC)	H02AB07

ATC: Anatomical Therapeutic Chemical classification system

Table S2. List of concurrent drugs reimbursed at index date and corresponding identification codes

Concurrent drugs at index date	Source	Code
Analgesics	Drug reimbursement (ATC)	N02
Antibiotics	Drug reimbursement (ATC)	J01
Anti-inflammatory	Drug reimbursement (ATC)	M01, M02
Respiratory/otological drugs	Drug reimbursement (ATC)	R01, R02, R05, R06, S01, S02

ATC: Anatomical Therapeutic Chemical classification system

Table S3. List of comorbidities at risk for glucocorticoid users and corresponding identification codes

Comorbidities	Source	Code
Diabetes	Hospital discharge summary or ALD registration (ICD-10) Drug reimbursement (ATC)	E10-E14 A10
Osteoporosis	Hospital discharge summary (ICD-10) Drug reimbursement (ATC)	M80-M81, M83-M85 M05BA, M05BB, M05BX04, M05BX03, G03XC01, H05BA, H05AA02
Psychotic disorders	Hospital discharge summary or ALD registration (ICD-10) Drug reimbursement (ATC)	F20-F29 N05A (N05AN excluded)

ALD: *Affection de Longue Durée* (chronic disease); ATC: Anatomical Therapeutic Chemical classification system; ICD-10: International Classification of Diseases 10th revision

Table S4. List of recognized indications of glucocorticoid therapy and corresponding identification codes

Indications	Sources	Codes
Cancer	Hospital discharge summary or ALD registration (ICD-10)	C00-C97, D00-D09, D37-D48
	Drug reimbursement (ATC)	L01, L02
Inflammatory bowel diseases	Hospital discharge summary or ALD registration (ICD-10)	K50, K51
	Drug reimbursement (ATC)	A07EA04, A07EC02, A07EC03, A07EC01, A07EA02, L04AB04, L04AB06, L04AC05, L04AX01
	Drug reimbursement (CIP)	3425409[a]
Multiple sclerosis	Hospital discharge summary or ALD registration (ICD-10)	G35
	Drug reimbursement (ATC)	L03AB07, L03AB08, L03AB13, L03AX13, L04AA27, N07XX07, N07XX09, L04AA31
Obstructive pulmonary diseases	Hospital discharge summary or ALD registration (ICD-10)	J44-J46, J96
	Drug reimbursement (ATC)	R03
Rheumatic diseases	Hospital discharge summary or ALD registration (ICD-10)	M05, M06, M08, M30-M35, M45, M46
	Drug reimbursement (ATC)	L04AA13, L04AA24, L04AB04, L04AB06, L04AB01, L04AB05, L04AC03, L04AC08, L04AC07, L04AD01, L04AX01, L04AX03, L01BA01[b], L01AA01, A07EC01, P01BA01, P01BA02, M01CB05, M01CC01
	Drug reimbursement (CIP)	3293907[c]

ALD: *Affection de Longue Durée* (chronic disease); ATC: Anatomical Therapeutic Chemical classification system; CIP: *Code d'identification de la présentation* (French nomenclature, unique identification code for each presentation of a proprietary medicinal product); ICD-10: International Classification of Diseases 10th revision

[a] No ATC code for para aminosalicylic acid labeled for inflammatory bowel diseases; it was identified using CIP code

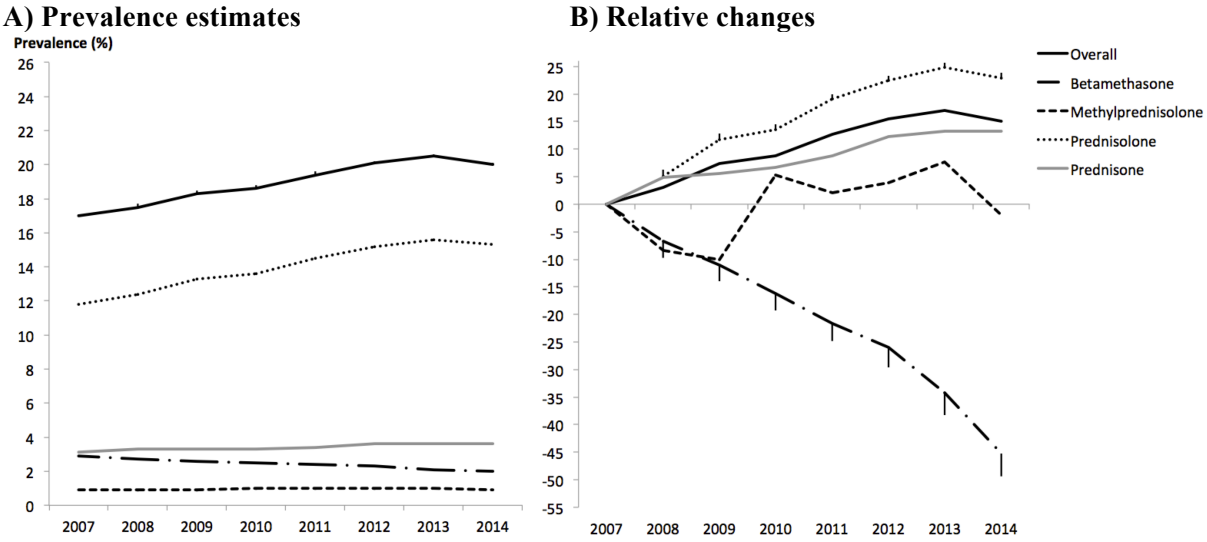
[b] The pharmaceutical forms of methotrexate labeled for oncology, identified using CIP codes (3150125, 3150148, 3160218), were excluded

[c] No ATC code for tiopronine labeled for rheumatoid arthritis; it was identified using CIP code (3293907)

Table S5. List of therapeutic measures associated with the prescription of glucocorticoids and corresponding identification codes

Therapeutic measures	Sources	Codes
Prevention/management of osteoporosis		
Dual-energy X-ray absorptiometry, DXA	Hospital discharge summary or ambulatory setting (CCAM)	PAQK007
Drugs for osteoporosis management	Drug reimbursement (ATC)	M80-M81, M83-M85 M05BA, M05BB, M05BX04, M05BX03, G03XC01, H05BA, H05AA02, A12AX, A12AA, A11CC
Potassium supplementation		
Potassium supplements	Drug reimbursement (ATC)	A12B
Serum potassium assay	Lab test, ambulatory setting (TNB)	1608, 1609, 1610
Ulcer prophylaxis		
Proton pump inhibitors	Drug reimbursement (ATC)	A02BC
Non-steroidal anti-inflammatory	Drug reimbursement (ATC)	M01A
Aspirin labeled for anti-inflammatory properties	Drug reimbursement (ATC)	N02BA01, N02BA51

ALD: *Affection de Longue Durée* (chronic disease); ATC: Anatomical Therapeutic Chemical classification system; CCAM: *Classification Commune des Actes Médicaux* (French medical classification for clinical procedures); TNB: *Table Nationale de Biologie* (French medical classification for lab tests)



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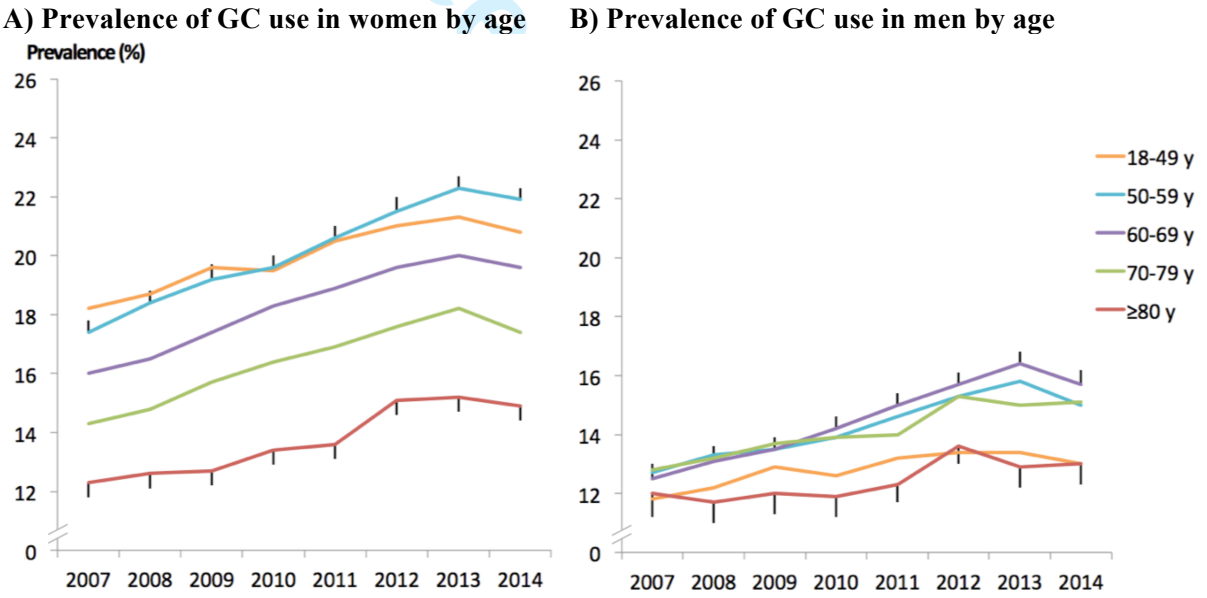

Figure S2. Trends in prevalence of oral glucocorticoid (GC) use in France per year from 2007 to 2014, in women (A) and men (B) according to age. Prevalence estimates with 95% CIs (error bars)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#4
Objectives	3	State specific objectives, including any pre-specified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#4 to 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	#5 to 6 Not applicable (NA) #5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#5 to 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#5 to 6
Bias	9	Describe any efforts to address potential sources of bias	#5
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#7
		(*b*) Describe any methods used to examine subgroups and interactions	#7
		(*c*) Explain how missing data were addressed	#7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#7 #8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Data available on request
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	#9 to 10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	#7 to 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	#8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	#10 to 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#12 to 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	#11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.