Severe Neuropsychiatric Outcomes Following Discontinuation of Long-Term Glucocorticoid Therapy: A Cohort Study

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ABSTRACT

Background: It has been estimated that, at any point in time, about 1% of the general adult population of the United Kingdom is receiving long-term (ie, ≥ 3 months) oral glucocorticoid therapy. These patients may develop neuropsychiatric disorders when the drug is discontinued.

Method: Data were obtained for all adult patients registered from January 1, 1990, through December 31, 2008, at UK general practices that were contributors to The Health Improvement Network database. Data from 21,995 adult patients who had been exposed to long-term oral glucocorticoids and who had discontinued the drugs after an exposure ranging from 1 to 3 years were analyzed. The within-person incidence rate ratios (IRRs) for Read codes and/or prescriptions for depression, delirium/confusion, mania, panic disorders, and suicide or suicide attempt during the withdrawal period were estimated using a self-controlled case series methodology. The predictors of the outcomes were ascertained using Cox proportional hazards models.

Results: The risk of depression (IRR = 1.13; 95% CI, 1.00–1.28; $P = .04$) and of delirium/confusion (IRR = 2.67; 95% CI, 1.96–3.63; $P < .001$) was significantly higher during the discontinuation period compared to a reference period defined as ranging from 5 to 3 months before the drug cessation. Older people were at higher risk of delirium/confusion. The use of long-acting glucocorticoids was associated with a higher risk of both depression (adjusted hazard ratio [HR] = 1.92; 95% CI, 1.07–3.46) and delirium/confusion (adjusted HR = 4.96; 95% CI, 2.60–9.49) during the withdrawal period.

Conclusions: Discontinuation of long-term glucocorticoid therapy is associated with an increased risk of both depression and delirium/confusion. People treated with long-acting glucocorticoids are particularly at risk.

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The association between endogenous glucocorticoid (ie, cortisol) and major neuropsychiatric disorders has been previously documented.[1–6] Such disorders have also been reported in people exposed to exogenous glucocorticoids (ie, glucocorticoid therapy). In patients prescribed glucocorticoids, the risk of depression, mania, delirium/confusion, panic attack, and suicide or suicide attempt within the first weeks of therapy is increased 2-fold to 7-fold when compared to people with the same underlying disease but who are not prescribed the drug.[7] On the other hand, the neuropsychiatric effects of withdrawal from long-term glucocorticoid therapy are poorly documented and are limited to a few cases reports.[8–15] Depression or delirium/confusion, sometimes associated with hypothalamic-pituitary-adrenal axis suppression, have been observed.[9–12] Glucocorticoid withdrawal–induced mania or panic attacks are less commonly reported.[13,14] Little is known about the incidence rate of and the risk factors for neuropsychiatric disorders following discontinuation of long-term glucocorticoid therapy.

Our aims were (1) to assess the incidence rates of neuropsychiatric outcomes in people stopping long-term glucocorticoid therapy, (2) to assess whether or not there was an increased risk of such outcomes during the glucocorticoid withdrawal period by comparing to a reference period, and (3) to ascertain the risk factors for developing these outcomes.

METHOD

Data Source: The Health Improvement Network

Approximately 98% of the population in the United Kingdom is registered with a general practitioner.[16] The Health Improvement Network (THIN) is a database of electronic medical records from general practices across the United Kingdom. Participating general practitioners systematically and prospectively retrieve and enter clinical information on patients, including demographic data, diagnoses, and prescriptions. The database hence provides a longitudinal medical record for each patient. The consultation and prescription data recorded in THIN compare favorably with national data, and prescribing is particularly well recorded since the practice computers are used by doctors to issue prescriptions. The THIN database has been previously validated through audits, comparisons to external statistics, and independent studies. This validation has shown that the database has a high level of completeness of clinical diagnostic and prescribing data.[17–21] To minimize any bias on disease occurrence and/or prescriptions issued, we restricted our analyses to high-quality data by using 3 quality indicators, as defined elsewhere.[22,23] We used data from January 1, 1990, to December 31, 2008, from 426 general practices. The study was approved by the THIN scientific review committee.

Study Population

In the THIN database, each drug is encrypted using Multilex codes that are associated with data from the *British National Formulary*.[24] We selected glucocorticoids prescribed orally, including prednisolone, prednisone, dexamethasone, triamcinolone, betamethasone, methylprednisolone,

Clinical Points

- Discontinuation of long-term glucocorticoid therapy is associated with an increased risk of both depression and delirium/confusion.
- Elderly people and those treated with long-acting glucocorticoids are at particular risk for glucocorticoid withdrawal–induced neuropsychiatric symptoms.
- An underlying adrenal insufficiency must be ruled out when neuropsychiatric symptoms are diagnosed in people discontinuing long-term glucocorticoid exposure.

and deflazacort. We included people aged 18 years and older and identified all who received at least 1 of these drugs for a period of 1 to 3 years and then stopped treatment before the end of their follow-up. We chose to include only people treated for 1 to 3 years to homogenize our study population. We also chose to select only people exposed for the first time to long-term glucocorticoid therapy to ensure that the probability of glucocorticoid withdrawal could not be affected by a previous history of withdrawal-induced neuropsychiatric disorders and thus to provide unbiased estimates. We calculated a mean daily dosage for each prescription by multiplying the number of tablets prescribed by the dose per tablet (calculated as prednisone equivalence[25,26]) and then dividing by the duration of the prescription. The date of treatment cessation was defined as the date of the last prescription plus the duration of the last prescription. Patients treated exclusively with topical, inhaled, or parenteral glucocorticoids were not included in the analyses. The medical diagnosis recorded on the date of starting glucocorticoids was used as the indication for the glucocorticoid prescription.

Identification of Neuropsychiatric Outcomes

All diagnoses and symptoms are recorded in THIN using the Read classification system.[27] Using the method described previously,[28] Read code lists were developed by the study team to identify recorded diagnoses of some neuropsychiatric disorders (eg, depressive disorder, manic disorder), recorded symptoms linked to a neuropsychiatric disorder (eg, low mood, delirium), or recorded prescription of an antidepressant, antipsychotic, or antimanic drug. For instance, patients were defined as depressed if they had a Read code entry for unipolar depression and/or symptoms linked to depression (eg, low mood) and/or a prescription for an antidepressant on a given consultation date. However, diagnoses were taken into account in the first place. Prescriptions of antidepressants were used as a definition of the outcome only when there was no recorded diagnosis of a neuropsychiatric illness and no other recorded indication for the prescription. We applied similar criteria to define 4 other neuropsychiatric outcomes. These were delirium/confusion (diagnosis or symptoms of delirium/confusion or prescription of antipsychotic medication), mania (diagnosis or symptoms of mania or prescription of antimanic medication), panic disorders (diagnosis of panic disorders or panic attack but excluding codes for anxiety), and suicidal phenomena (diagnosis of suicide or suicide attempt). To constitute a new episode, there had to be a preceding gap of at least 6 months of no similar entry (ie, no coded entries for diagnosis, symptom, or medication linked to the diagnosis).

Statistical Analysis

Five periods of 2 months each were defined, ranging from 5 months before to 5 months after the supposed end date of glucocorticoid therapy. The withdrawal period was defined as 1 month before to 1 month after the supposed end date of treatment.

Using the whole sample of people discontinuing long-term glucocorticoid therapy, we started by calculating incidence rates of each neuropsychiatric outcome during each of the 5 time periods. Incidence rates were assessed by dividing the number of newly diagnosed cases of neuropsychiatric outcome by the total follow-up time at risk. We censored patients at their first event if they had several events.

We then used the self-controlled case series methodology to assess the relative incidence rate ratios (IRRs) of neuropsychiatric outcomes during the withdrawal period in comparison to a reference period. For this assessment, we used data only from individuals who had experienced both glucocorticoid withdrawal and the outcome of interest (ie, a neuropsychiatric disorder). The self-controlled case series methodology relies on within-person comparisons.[29,30] Inference is within individuals, meaning that the potential confounding effect of both recorded and unrecorded fixed characteristics that vary between individuals is removed. The period ranging from 5 to 3 months before the drug cessation was chosen as the reference period since, during this time period, people had been receiving glucocorticoids for many months and were still receiving a substantial daily dosage (ie, around 10 mg/d). Therefore, we considered it to be unlikely that those people would experience either a glucocorticoid-induced or a withdrawal-induced neuropsychiatric disorder during this time period.

Finally, we again used the whole sample of individuals discontinuing glucocorticoids to examine which factors were associated with the outcomes that showed increased risk of occurring during the withdrawal period. In this analysis, we compared people who reported the outcome during the withdrawal period with those who did not report the outcome during this time period. For this analysis we used Cox proportional hazards models. The models were adjusted for gender, age (classified into 4 categories), past history of neuropsychiatric disorder (defined as a record of depression, delirium/confusion, mania, or panic disorders in the medical file of patients before any exposure to systemic glucocorticoid therapy), duration of glucocorticoid exposure (continuous variable), and type of prescribed glucocorticoid (short-acting versus long-acting[24]). Proportional hazard assumptions were checked graphically.

Continuous variables are presented as median and 25th to 75th percentile values, and categorical variables are presented

Table 1. Incidence Rates of Neuropsychiatric Outcomes (per 100 person-years at risk) (N = 21,995)

Variable	Before Glucocorticoid Cessation				**Withdrawal Period[a]**		After Glucocorticoid Cessation			
	5 to Just Over 3 Months Before Glucocorticoids Are Stopped		3 to Just Over 1 Month Before Glucocorticoids Are Stopped		**1 Month Before to 1 Month After Glucocorticoids Are Stopped**		Just Over 1 to 3 Months After Glucocorticoids Are Stopped		Just over 3 to 5 Months After Glucocorticoids Are Stopped	
Daily dosage of prednisone equivalent at the beginning of the period, median (IQR), mg	9 (5–15)		8 (4–14)		**5 (2–9)**		NA		NA	
	IR	95% CI	IR	95% CI	**IR**	**95% CI**	IR	95% CI	IR	95% CI
Depression	9.9	8.9–11.0	10.6	9.5–11.7	**11.1**	**10.0–12.3**	10.1	8.9–11.4	10.2	9.0–11.7
Delirium/confusion	1.5	1.2–2.0	2.0	1.6–2.5	**3.9**	**3.3–4.6**	1.8	1.4–2.4	1.5	1.0–2.0
Mania	0.3	0.1–0.5	0.3	0.1–0.5	**0.4**	**0.2–0.7**	0.2	0.1–0.5	0.2	0.1–0.5
Panic disorders	0.5	0.3–0.8	0.3	0.2–0.5	**0.4**	**0.3–0.7**	0.4	0.2–0.8	0.4	0.2–0.8
Suicide or suicide attempt	0.05	0.01–0.21	0.05	0.01–0.21	**0.03**	**0.01–0.20**	0.0	NA	0.04	0.01–0.31

[a]Boldface type is used to accentuate the time period of primary interest.
Abbreviations: IQR = interquartile range, IR = incidence rate, NA = not applicable.

Table 2. Association Between Withdrawal From Long-Term Glucocorticoid Treatment and Neuropsychiatric Outcomes[a]

Outcome and Time Period[b]	Incidence Rate Ratio	95% CI	*P*
Depression			
Reference period	1		
Withdrawal period	1.13	1.00–1.28	.04
Delirium/confusion			
Reference period	1		
Withdrawal period	2.67	1.96–3.63	< .001
Mania			
Reference period	1		
Withdrawal period	1.73	0.79–3.82	.18
Panic disorders			
Reference period	1		
Withdrawal period	0.91	0.47–1.76	.77
Suicide or suicide attempt			
Reference period	1		
Withdrawal period	0.62	0.06–6.92	.70

[a]Self-controlled case series analysis; n = 991 (ie, 540 patients with a neuropsychiatric outcome during the withdrawal period and 451 patients with a neuropsychiatric outcome during the reference period).
[b]Reference period was from 5 to 3 months before discontinuation.

as proportions and 95% CIs. Incidence rates are reported per 100 person-years at risk. All analyses were done using Stata statistical software, version 11.1 (StataCorp; College Station, Texas).

RESULTS

Study Population

Overall, 26,155 oral glucocorticoid courses lasting from 1 to 3 years were prescribed in 21,995 patients aged 18 years and over (13,714 women; 62.4%). Patients' median age at first long-term glucocorticoid course discontinuation was 72.6 years (interquartile range [IQR], 61.3–80.5 years), and the median duration of the glucocorticoid course was 524 days (IQR, 434–814 days). Glucocorticoid treatment was mainly prescribed for polymyalgia rheumatica and/or giant cell arteritis (n = 6,461; 29.4%), asthma (n = 3,333; 15.2%), chronic obstructive pulmonary disease (n = 2,508; 11.4%), or rheumatoid arthritis (n = 2,066; 9.4%). Prednisolone (n = 21,482; 97.7%), dexamethasone (n = 304; 1.4%), betamethasone (n = 85; 0.4%), and prednisone (n = 59; 0.3%) were the main drugs prescribed.

Incidence of Neuropsychiatric Outcomes in the Full Cohort

We identified 2,080 incident cases of neuropsychiatric outcomes within the period ranging from 5 months before to 5 months after the actual cessation of glucocorticoid therapy (depression: n = 1,604 [77.1%]; delirium/confusion: n = 355 [17.1%]; panic disorders: n = 68 [3.3%]; mania: n = 47 [2.2%]; and suicide or suicide attempt: n = 6 [0.3%]). Among these cases, 540 (26.0%) occurred during the withdrawal period. Incidence rates per 100 person-years at risk during the withdrawal period were 11.1 (95% CI, 10.0–12.3) for depression, 3.9 (95% CI, 3.3–4.6) for delirium/confusion, 0.4 (95% CI, 0.2–0.7) for mania, 0.4 (95% CI, 0.3–0.7) for panic disorders, and 0.03 (95% CI, 0.01–0.20) for suicide or suicide attempt (Table 1).

Self-Controlled Case Series Analysis in Patients With Neuropsychiatric Outcomes

Patients who suffered from a neuropsychiatric outcome during the 2-month withdrawal period (n = 540) or the 2-month comparison period (n = 451) were eligible for the self-controlled case series analysis. The withdrawal period was associated with an increased risk of depression (IRR = 1.13; 95% CI, 1.00–1.28; $P = .04$) and of delirium/confusion (IRR = 2.67; 95% CI, 1.96–3.63; $P < .001$). There was no increase in risk for mania, panic disorders, and suicide or suicide attempt (Table 2).

Risk Factors in the Full Cohort

Depression associated with discontinuation of long-term glucocorticoid therapy was more frequently observed in people with a past history of depression, while age, gender, and duration of glucocorticoid exposure did not predict this outcome (Table 3). The risk of delirium/confusion was higher in older patients (see Table 3). Compared to people exposed to short-acting glucocorticoids (ie, prednisone, prednisolone, methylprednisolone, deflazacort), those exposed to long-acting molecules (ie, dexamethasone, betamethasone, triamcinolone) were more at risk of suffering from both depression (adjusted hazard ratio [HR] = 1.92; 95% CI, 1.07–3.46) and delirium/confusion

Table 3. Risk Factors for Withdrawal-Induced Neuropsychiatric Disorders (N = 21,995)

	Depression			Delirium/Confusion		
Variable	Hazard Ratio[a]	95% CI	*P*	Hazard Ratio[a]	95% CI	*P*
Sex						
Women	1			1		
Men	0.98	0.79–1.22	.87	1.37	0.96–1.94	.08
Age, y						
18–39	1			1		
40–59	1.03	0.58–1.84	.91	0.38	0.11–1.31	.13
60–79	1.38	0.81–2.36	.24	1.63	0.64–4.11	.30
≥ 80	1.53	0.88–2.66	.13	3.88	1.54–9.75	.004
Past medical history[b]						
Depression	1.79	1.45–2.21	< .001	0.46	0.30–0.71	< .001
Delirium/confusion	0.88	0.53–1.49	.64	1.76	0.92–3.37	.09
Mania	1.26	0.75–2.12	.39	1.51	0.62–3.72	.37
Panic disorders	1.53	0.98–2.37	.06	1.14	0.36–3.63	.83
Duration of glucocorticoid therapy per each increased month	1.00	0.99–1.02	.57	1.00	0.98–1.02	.93
Type of glucocorticoid therapy						
Short-acting[c]	1			1		
Long-acting[d]	1.92	1.07–3.46	.03	4.96	2.60–9.49	< .001
Underlying disease						
Asthma	1			1		
Chronic obstructive pulmonary disease	1.20	0.82–1.77	.36	1.35	0.65–2.81	.42
Polymyalgia rheumatica and/or giant cell arteritis	0.96	0.69–1.34	.82	0.89	0.46–1.70	.72
Rheumatoid arthritis	0.95	0.61–1.47	.81	1.36	0.61–3.04	.45
Other	1.00	0.72–1.38	.99	1.65	0.90–3.01	.11

[a]Value of 1 indicates reference category. [b]Before glucocorticoid initiation. [c]Prednisolone, prednisone, methylprednisolone, deflazacort. [d]Dexamethasone, betamethasone, triamcinolone.

(adjusted HR = 4.96; 95% CI, 2.60–9.49) during the withdrawal period.

DISCUSSION

We found that discontinuation of long-term glucocorticoid therapy is associated with a slightly increased risk of depression and a higher risk of delirium/confusion. Patients exposed to long-acting glucocorticoids are more likely to suffer from withdrawal-induced neuropsychiatric outcomes compared to patients exposed to short-acting molecules.

It has been estimated that, in 2008, about 1% of the UK population was receiving long-term (ie, ≥ 3 months) glucocorticoid therapy at any time.[31] Neuropsychiatric symptoms are frequently observed in these individuals. The symptoms occur mainly within the first weeks of therapy.[32] After 3 months of treatment, half of glucocorticoid-exposed patients report neuropsychiatric adverse events.[33] These neuropsychiatric events (eg, anxiety, irritability, euphoria, insomnia) are often of low or mild severity but are cited by patients as the second most distressing type of glucocorticoid-induced adverse event after morphological changes.[33] However, some neuropsychiatric adverse events are life-threatening. For instance, in comparison with people suffering from the same disease but who were not exposed to glucocorticoids, those exposed to oral glucocorticoids had a 2-fold increased risk of depression, a 4- to 5-fold increased risk of mania or delirium/confusion, and a 7-fold increased risk of suicide within the first weeks of glucocorticoid therapy.[7]

Patients undergoing extended glucocorticoid therapy frequently develop withdrawal symptoms when the treatment is stopped, including diverse symptomatic patterns such as fatigue, depression, or psychosis. As early as 1951, Freyberg et al[34] had described a glucocorticoid withdrawal syndrome characterized by fatigue, anorexia, discouragement, and depression in 20% of patients with rheumatoid arthritis. More recently, hematology patients exposed to long-term glucocorticoid therapy withdrawal reported that they experienced a stressful and emotionally challenging time.[13] However, literature about neuropsychiatric disorders after discontinuation of long-term glucocorticoid therapy is limited to case reports.[9–15] For some of these patients, the depression or delirium symptoms occurred within the context of an underlying hypothalamic-pituitary-adrenal axis suppression,[9–11] and, interestingly, we found that patients exposed to long-acting glucocorticoids (ie, those inducing a longer suppression of the hypothalamic-pituitary-adrenal axis) were more at risk of withdrawal-induced depression and delirium/confusion. However, the glucocorticoid withdrawal–induced neuropsychiatric symptoms are not always synonymous with underlying adrenal insufficiency. Glucocorticoids have direct and indirect effects on the brain,[1,5] and human and animal studies have indicated that chronic glucocorticoid exposure may cause cerebral atrophy, loss of neurons, and inhibition of neuronal regeneration.[35–39] Moreover, glucocorticoids dysregulate the brain serotonin system, which has been implicated in the control of behavioral processes and neuropsychiatric disorders such as depression and anxiety.[40–42] The hippocampus contains particularly high concentrations of glucocorticoid receptors and has been frequently reported to be damaged by glucocorticoids,[37,38,41–45] even though some contradictory results have been published.[46] Some of these pathophysiologic

mechanisms may intervene, at least partly, in the glucocorticoid withdrawal–induced neuropsychiatric disorders not associated with adrenocortical insufficiency.

The study population was elderly, reflecting the population prescribed long-term glucocorticoid therapy in the general population. Because older people are particularly at risk for withdrawal-induced delirium/confusion, we suggest that physicians should be vigilant when they discontinue glucocorticoids in elderly patients. Accurate information should be disclosed to the patient and the family so as to diagnose and treat any neuropsychiatric symptoms as early as possible.

Our study has several strengths, including the very large, population-based, unselected population of patients of both sexes and all adult age groups and with a wide range of diseases. Moreover, our findings are relevant to general practitioners' clinical practice, as we report outcomes associated with diagnostic labels used in general practice rather than strict *DSM-IV* or *ICD-10* classifications. However, there are some limitations. In THIN, neither the true cessation date of a treatment nor data on adherence to treatments are available. We defined the end of glucocorticoid therapy as the date on which the drugs issued on the last prescription would have been fully used. However, in a few instances, some individuals might have tapered their glucocorticoid therapy for several weeks prior to this date, and others may still have been receiving glucocorticoids beyond the defined cessation date. To try to overcome these inaccuracies, we chose to define the withdrawal period as a 2-month period surrounding the supposed end date of the treatment. However, the effect of using a wide exposure risk period due to the unknown true date of cessation may have biased the IRR estimates toward the null.

Second, we calculated a mean daily dosage of prednisone equivalent per each period of interest since it was impossible to define the exact daily dosage received at the beginning of each time period. The daily dosage was estimated by dividing the number of tablets prescribed by the duration of the prescription. In some cases, the duration of the prescription lasted several weeks. Using these means rather than the exact daily dosage may have led to a degree of imprecision.

Third, we chose to use diagnoses and drug prescriptions to define cases of depression, delirium/confusion, and mania. However, in some cases, medications may have been prescribed for other conditions (eg, antidepressants for neuropathies). It is possible that this choice led to a slight overestimation of incidence rates of neuropsychiatric outcomes. However, we also feel that these rates would have been underestimated if medication prescriptions were not taken into account. Indeed, we believe that physicians are less likely to record a diagnosis of a neuropsychiatric illness they attribute to glucocorticoid withdrawal and for which they know that the symptoms will improve within a few days or weeks after glucocorticoid cessation.

Fourth, it is likely that some neuropsychiatric symptoms occurred in the context of a concomitant adrenocortical insufficiency, but this hypothesis cannot be assessed using THIN data.

Last, the neuropsychiatric disorders that occurred during the withdrawal period may have been the consequence of, but also the cause of, glucocorticoid discontinuation. However, in our opinion, the neuropsychiatric disorders are much more likely to be the consequence since (1) all the patients included in this study were chronically exposed to glucocorticoids, (2) glucocorticoid-induced neuropsychiatric disorders (which may have led to withdrawal of the drug) are usually observed within the first weeks of exposure rather than after several months of treatment, and (3) the mean dosage of prednisone equivalent during the withdrawal period was low (ie, around 5 mg/d), while glucocorticoid-induced neuropsychiatric disorders are more frequently observed during high-dosage exposure.

In conclusion, discontinuation of long-term glucocorticoid exposure is associated with an increased risk of depression and delirium/confusion. This association is worse with long-acting glucocorticoids, which should therefore be used with caution. We suggest that physicians who observe these disorders in patients after glucocorticoid discontinuation should first rule out adrenocortical insufficiency. If adrenal insufficiency were to be identified, readministration of glucocorticoids would help to resolve the symptoms.[9–11] In cases for which adrenal insufficiency is ruled out, the best management approach remains undetermined, and further research is required on the best preventive or curative treatment of these disorders.

Drug names: betamethasone (Celestone, Diprolene, and others), dexamethasone (Dexamethasone Intensol and others), methylprednisolone (Medrol and others), prednisolone (Prelone, Orapred, and others), prednisone (Rayos and others), triamcinolone (Kenalog and others).

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Author contributions: Dr Fardet designed the study, performed the statistical analyses, and wrote the initial draft of the manuscript. Dr Nazareth designed the study and revised the manuscript. Dr Whitaker provided advice for the statistical analyses. Dr Petersen designed the study, supervised the statistical analyses, and revised the manuscript.

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