ORIGINAL ARTICLE

Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information

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Summary

Objective Appropriate self-management of glucocorticoid therapy (GC) is crucial for patients with adrenal insufficiency (AI). We aimed to describe patients' self-reported nonadherence to GC, evaluate perceived doubts about need for GC, concerns about adverse effects, and dissatisfaction with information received about GC.

Design Cross-sectional survey.

Patients Patients prescribed GC for AI ($n = 81$) from five European countries.

Measurements Online survey including the Medication Adherence Report Scale (MARS), Beliefs about Medicines Questionnaire© (BMQ Specific, adapted for AI) and Satisfaction with Information about Medicines Scale© (Prof Rob Horne; SIMS).

Results Most patients (85·2%) reported a degree of nonadherence to GC. The most frequent types of nonadherence concerned changing the timing of GC doses, for example taking a dose later in the day than advised (37·0%). Few patients doubted their personal need for daily GC, but most reported high concerns about GC including potential weight gain (50·6%), osteoporosis (53·6%) and the continuing risk of adrenal crisis (50·6%). Dissatisfaction with information about GC was frequent, with participants particularly dissatisfied with the amount of information they had received about potential problems with GC. People who expressed dissatisfaction with information about GC, and concerns about its adverse effects were also more likely to report nonadherence ($P < 0·05$).

Conclusions Nonadherence to treatment, concerns about potential adverse effects and dissatisfaction with the information provided about treatment were frequently reported by this European sample of AI patients. Many AI patients may need additional information about their GC and support to address concerns about GC and facilitate adherence.

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Introduction

A replacement medication regimen including glucocorticoid and mineralocorticoids is essential for patients with adrenal insufficiency (AI).[1] However, some patients do not take their treatment as prescribed putting them at risk of adrenal crises and ill health.[2,3] Existing steroid replacement regimens are complex and usually require patients to take medication at specific times of the day to mimic normal physiological cortisol rhythm.[3] Education is important, and patients learn how to increase their medication in response to physiological exertion, psychological stress and minor illness.[1,4] Despite recognition by patients and practitioners of the importance of adherence to glucocorticoid therapy (GC) replacement, little is known about the adherence of patients to GC treatment and less about why patients may not take medication in the optimal way.

Few studies have addressed adherence in patients with AI. One recent survey of 116 Dutch AI patients found that reported adherence to treatment advice was suboptimal in three domains: adherence to medication, preparedness for an adrenal crisis (e.g. carrying an ampoule of hydrocortisone) and dose adaptation in medical emergencies.[5] Reasons for nonadherence are complex and may not always be recognized by clinicians. For those involved in clinical patient management and HCPs advising on treatment regimens an understanding of patient's perceptions is important. Despite this, few studies have explored AI patients' perceptions of treatment and adherence using the validated questionnaires often used to assess these factors in other long-term conditions. A single published study assessed patients' beliefs about medications used to treat AI and found that patients were often concerned about the potential adverse effects of their medication.[6] Across over 23 other long-term conditions (e.g. HIV, asthma, diabetes, hypertension), doubts about personal need for treatment and concerns about treatment have been frequently linked to nonadherence, with those with greater concerns being less likely to adhere to their prescribed treatment

regimen.[7] However, no studies have explored the relationship between adherence to treatment, beliefs about treatment and information in AI.

This study uses validated questionnaire methods to explore perceptions of GC (perceived need for treatment and concerns about adverse effects) and reported nonadherence in AI. Because information provision may be one way to address concerns and enable patients to adhere, for example if they receive education on adverse effect risks and how to take their medication, we also use a validated scale to assess satisfaction with information about GC. As adherence to GC medication requires not only taking a certain number of doses (dose adherence) but also requires that these doses are taken at particular times (timing adherence), we also examined patients' reports of their adherence to each of these different aspects of adherence.

Recognizing that understanding reasons behind nonadherence is essential in the management of patients with AI, this study addressed the following aims:

1 To identify the prevalence and nature of self-reported nonadherence (including both dose adherence and timing adherence)

2 To understand AI patients' perceptions of GC and satisfaction with information that they have received about GC

3 To test whether reported nonadherence is correlated with negative views about GC (doubts about GC necessity, GC concerns and dissatisfaction with information about GC).

Method

Design

This is a cross-sectional survey of AI patients, in which questionnaires validated for assessing patients' perceptions of treatment and reported adherence to treatment in other long-term conditions were adapted for use in AI.

Recruitment

Participants were recruited in May 2013 across five European countries (UK, Germany, Sweden, France and Spain) through convenience sampling. Patient support groups (e.g. the Pituitary Foundation and Addison's Disease Network) and endocrinology consultants were asked to make AI patients known to them aware of the opportunity to participate in the study, including being provided with the contact details of the research team. Patients already registered with market research databases were also contacted. Where possible, posts were made on social media and patient forums to raise awareness of the study. Patients who made contact with the research team were screened by a market researcher to ensure they met the inclusion/exclusion criteria; eligible patients were sent a link to the online survey. All participants who assessed as being eligible by the screening procedure participated in and completed the survey. The Market Research Society (MRS) approved the patient enrolment procedure. Consent was obtained using an online form immediately prior to data collection. Participants were paid for completing the survey:

UK: £35, France €25, Germany €45, Italy €40, Spain €40 and Sweden 200kr.

Inclusion/exclusion criteria

Participants were included if they were aged between 18 and 70 years, diagnosed with either primary AI (Addison's Disease), Secondary AI or Congenital Adrenal Hyperplasia (CAH). All participants had been diagnosed for more than 6 months, were taking hydrocortisone immediate release tablets (once, twice or three times daily), once-daily modified release hydrocortisone or cortisone acetate (once, twice or three times daily) for AI, with a sample quota of 50% to have been on treatment for 12 months or over. All participants also had computer access as needed to complete the survey.

Measures

Demographic and clinical information. Participants were asked to report their age, gender, type of AI (primary AI, secondary AI or CAH), and how many years they have been diagnosed with AI. Regarding their medication, participants were asked to describe their current GC, including the length of time they had been taking it. We also asked participants to report: recent days of illness and healthcare seeking; whether they had hypothyroidism, osteoporosis, type 1 diabetes, vitamin B12 deficiency or coeliac disease; and what medications they were taking for these or other comorbid conditions.

Adherence to steroid replacement therapy (GC). Participants rated their adherence to GC on an 8-item Medication Adherence Report Scale (MARS)© (Prof Rob Horne), modified for AI.[8] The four core items of the MARS were supplemented with four AI-specific items generated in discussion with clinicians and patients who formed the advisory panel. The revised 8-item scale had adequate internal reliability in the current sample (Cronbach's α = 0·86). Two subscales, one comprised of the five items concerning nonadherence to number of doses (Dose Adherence) and one comprised of the three items concerning deviations from the prescribed timing of doses (Timing Adherence), were used to describe the nature of nonadherence. Participants rated the frequency with which they performed each type of nonadherent behaviour on a 5-point scale (5 = never, 4 = rarely, 3 = sometimes, 2 = often and 1 = very often). Scores were summed to give a total score (range 8–40); higher scores indicate higher reported adherence.

To describe adherence, total scores and subscale scores were used to split participants in two ways: (i) full adherence (reporting no nonadherent behaviours) *vs* any reported nonadherence and (ii) high adherence (scoring more than 32, i.e. 80%) *vs* low adherence (scoring 32 or less). Individual item responses were also dichotomized (low adherence = sometimes, often or very often; high adherence = never, rarely), to provide an indication of the prevalence of each nonadherent behaviour.

Perceptions of GC. The Beliefs about Medicines Questionnaire (BMQ)©-Specific scale,[9] modified for AI was used to measure participants' beliefs about GC. The modified BMQ AI Specific© comprises: (i) a 5-item GC-Necessity subscale assessing the participant's views about their personal need for the GC medication; and (ii) an 11-item GC-Concerns subscale assessing participants' concerns about the potential adverse consequences of taking GC. The GC-Concerns subscale was adapted for AI with additional items about side effects, osteoporosis, weight gain, sleep, viewing GC as a reminder of AI and adrenal crises. For each BMQ statement, participants indicated their agreement on a 5-point Likert scale (range 1 = strongly disagree to 5 = strongly agree). GC-Necessity and GC-Concerns scores were computed by summing all subscale responses, then dividing by the number of items (range 1–5). In the current sample, both scales had good internal reliability (both Cronbach's α's = 0·86). To describe the frequency of individual concerns and doubts about GC necessity, we categorized participants on each GC-Necessity item (strongly disagree/disagree/uncertain = doubt; agree/strongly agree = no doubt) and GC-Concern item (agree/strongly agree = concern; strongly disagree/disagree/uncertain = no concern).

Satisfaction with information about GC. Participants completed the validated Satisfaction with Information about Medicines Scale© (SIMS),[10] to indicate their satisfaction with the information they had received about their GC. The SIMS has two subscales. The first assesses satisfaction with the information received about the Action and Usage of GC: about how it works and should be used, for example how to refill a prescription (SIMS AU 9-items). The second assesses satisfaction with information about dealing with Potential Problems associated with GC, for example adverse effects and interactions, (SIMS PP 8-items). For each subscale item, participants stated whether they were satisfied with the amount of information they had received (about right, none needed) or dissatisfied (too much, too little, none received). Subscale scores were calculated by counting the total number of 'satisfied' responses.

Statistical analyses

Descriptive statistics (means, standard deviations (SD) and frequencies) are used to describe responses to all items. Correlations are used to test for associations between BMQ, SIMS and MARS scales, and between MARS scores and participant age and time since diagnosis. Chi-square test is used to describe associations between categorized MARS scores and categorical variables (gender, type of AI, dose frequency).

Results

Demographics and patient characteristics

The sample comprised 81 participants from the UK (*n* = 20), France (*n* = 20), Sweden (*n* = 15), Spain (*n* = 16) and Germany (*n* = 10). All participants who expressed interested in taking part completed the survey. The mean age of the sample was 47·3 years (SD = 14·4 years). The sample was approximately two-thirds female (67·9%, *n* = 55).

Most participants had Primary AI. The mean length of time since diagnosis of AI was 12·2 years (SD = 8·7 years). Slightly under half of the sample reported at least one comorbid condition (see Table 1). Just over half the participants (51·9%, *n* = 42) reported that they had missed one or more days from study or work or had been unable to carry out their normal daily activities due to illness in the last year. Just under a quarter (22·2%, *n* = 18) had been to hospital due to an adrenal crisis in the past year, most of these (*n* = 13) on one occasion. The majority of these patients (*n* = 12, 14·8%) had only been to hospital on one occasion.

Most participants were taking twice (45·7%, *n* = 37) or three times daily (37·0%, *n* = 30) doses of hydrocortisone tablets. Eleven participants (13·6%) were taking modified-release, once daily hydrocortisone tablets. Only seven participants (8·6%) had changed their medication in the previous 2 years. Most (63·0%, *n* = 51) participants reported they had increased their GC dose in the past year due to illness. Over a third had increased their dose on 1–4 occasions (38·3%, *n* = 31), 17·3% (*n* = 14) had increased their dose 5–10 times and 7·4% (*n* = 6) had increased their dose more than 10 times. Approximately a quarter of the sample had been to hospital to receive intravenous hydrocortisone (24·7%, *n* = 20) and just under one in ten had self-administered intramuscular hydrocortisone in the past year (8·6%, *n* = 7). Of the 17 participants with Secondary AI, nine indicated they were taking thyroxine treatment for TSH deficiency, two were taking testosterone replacement therapy for gonadotropin deficiency, and four had growth hormone deficiency on replacement.

Prevalence and nature of nonadherence to GC

Only 12 (14·8%) reported full adherence, that is that they never took their medication in a way that was different to how it had

Table 1. Clinical characteristics of the sample

	n (%)
Type of adrenal insufficiency (AI)	
Primary (Addison's disease, congenital adrenal hyperplasia, autoimmune polyglandular syndrome)	64 (79·0%)
Secondary (caused by pituitary or hypothalamic disorder)	17 (21·0%)
Length of time with AI	
1–5 years	24 (29·6%)
6–10 years	17 (21·0%)
11–20 years	26 (32·1%)
21 or more years	14 (17·3%)
Comorbid conditions	
Hypothyroidism	31 (38·3%)
Osteoporosis	8 (9·9%)
Type 1 diabetes	6 (7·4%)
Vitamin B12 deficiency	6 (7·4%)
Coeliac disease	2 (2·5%)

been prescribed. Approximately one-third of participants (34·6%, $n = 28$) were in the low adherence group and (65·4%, $n = 53$) were classed as high adherers. This nonadherence arose from both dose and timing nonadherence; 79·0% of our sample reported any dose nonadherence ($n = 64$), and 66·7% ($n = 54$) reported any timing nonadherence. The most frequently reported individual nonadherent behaviours were associated with timing of doses. Over a third (37·0%, $n = 26$) said that they sometimes, always or often took their dose later in the day than advised, and 34·6% ($n = 28$) said that they sometimes, always or often took their dose at a different time of day than advised (see Fig. 1).

Perceptions of GC and satisfaction with information about GC

GC necessity beliefs. Participants' responses indicated that they were largely convinced of their personal need for their GC (BMQ Necessity mean = 4·61, SD = 0·66, scores near five indicate high Necessity). When responses to the individual items were assessed, the highest proportion of doubts were for the statement 'my health in the future will depend on my medicines', which 16·0% ($n = 13$) of respondents expressed doubt about. However, fewer than 10% of participants reported doubts about any other Necessity item, indicating that participants were typically strongly convinced of their current need for their medication (see Fig. 2).

GC concerns. Concerns about the *possible* adverse consequences of AI medication were prevalent (BMQ Concerns mean = 2·89, SD = 0·83, scores near one indicate high Concern). Most strikingly, 55·6% ($n = 45$) said that they 'sometimes worry about the long-term effects of this medication'; 53·1% ($n = 43$) agreed that they 'worry about medication causing osteoporosis'; 50·6% ($n = 41$) said that they worry that their medication 'might cause weight gain'; and 50·6% ($n = 41$) said that they 'worry about having an adrenal crisis despite taking my medication' (see Fig. 3).

Satisfaction with information about GC. Participants were more dissatisfied with the amount of information they had received about potential problems with their GC (SIMS PP mean

number of items rated as 'dissatisfied' = 3·94, SD = 2·84), than with the amount of information they received about the action and use of their GC (SIMS AU mean number of items rated as 'dissatisfied' = 2·79, SD = 3·08). Nearly two-thirds of participants were dissatisfied with the level of information they had received about the risks of getting side effects (61·7%, $n = 50$) and whether the medicine has unwanted side effects (59·3%, $n = 48$). More than half were dissatisfied with the amount of information they had received about whether they should drink alcohol while taking their AI medication (54·3%, $n = 44$), what they should do if they experience unwanted side effects (55·6%, $n = 45$), and about possible interactions with other medications (54·3%, $n = 44$) (see Fig. 4).

Was reported nonadherence associated with clinical and demographic factors?

Demographic factors were associated with adherence, such that women were more likely to report low adherence than men, 41·8% of female participants reported low adherence compared to 19·2% of male participants $\chi^2(1, n = 81) = 3·98$, $P = 0·05$, and age was associated with adherence such that older participants were more adherent, $r(81) = 0·45$, $P < 0·001$. The distribution of adherence scores was similar across participants who did and did not report comorbidities and those reported primary *vs* secondary AI ($ps > 0·05$). To investigate the impact of dosing frequency, we compared MARS scores in participants who reported taking one or two doses of GC each day with participants who reported three or more daily doses using a Mann–Whitney U-test. Participants who reported one or two daily doses were more adherent than participants who took 3 or more doses $U = 518·50$, $P = 0·04$.

Was reported nonadherence associated with doubts about GC necessity, GC concerns and dissatisfaction with information about GC?

To test whether reported nonadherence is associated with negative views about GC (doubts about GC necessity, GC concerns and dissatisfaction with information about GC), Spearman's correlations were computed between MARS scores, BMQ scores and SIMS scales. Higher reported nonadherence on the MARS
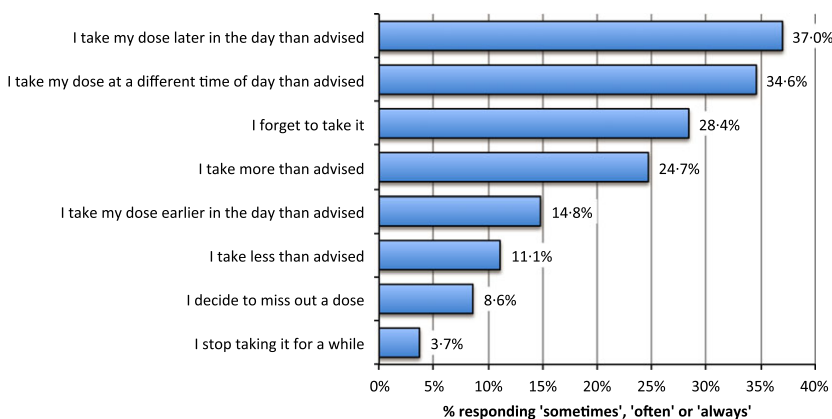

Fig. 1 Prevalence of nonadherent behaviours based on proportion of participants who report that they 'sometimes, often or always' took their regimen in ways other than advised when responding to the MARS scale.

Fig. 2 Doubts about need for glucocorticoid therapy (GC). Percentage of respondents endorsing 'uncertain', 'disagree' or 'strongly disagree' to statements about their personal need for their GC.
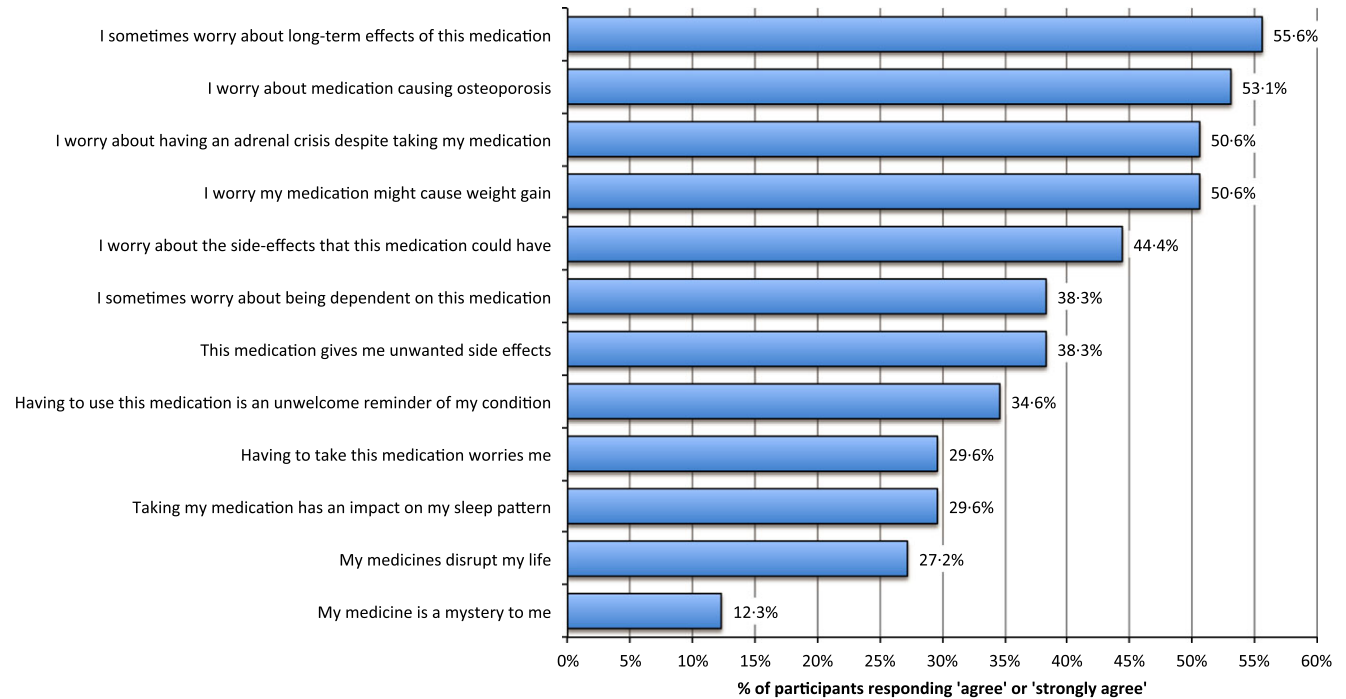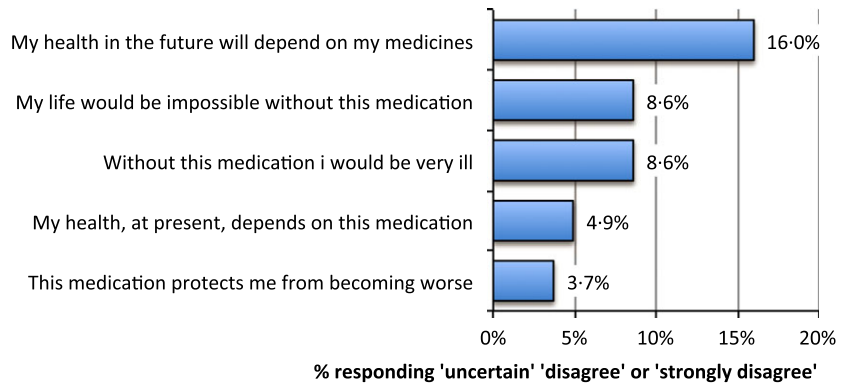

Fig. 3 Glucocorticoid therapy (GC) concerns. Percentage of respondents endorsing 'agree' or 'strongly agree' to statements about concerns about GC.

was significantly associated with more GC Concerns and more dissatisfaction with information (SIMS AU and SIMS PP; see Fig. 5). GC Necessity was not significantly associated with adherence.

Discussion

This study is the first to examine AI patients' adherence to GC and to explore associations between adherence and perceptions of treatment. We found only 12·8% reported full adherence. Few patients doubted their personal need for daily GC, but many had strong concerns about the potential adverse effects of GC and were dissatisfied with the amount of information about GC they had received. People who were dissatisfied with the amount of information they had received and concerned about the potential negative effects of GC reported more nonadherence to GC.

Significant numbers of participants reported nonadherent behaviours, with fewer than 15% of patients reporting they always took their medication as prescribed. Analysis of the MARS item scores indicated particular difficulties with taking treatment on time, with a third of patients reporting they varied their medication schedule and a third stating that they delayed doses. Out findings supplement existing literature which suggests that patients may forget daily doses[11] and that adjusting doses when at risk of adrenal crisis may be a particular challenge for patients.[5] This indicates that even when patients are taking the recommended number of doses they may be taking a proportion of these doses off-schedule. Non-adherence to GC may place participants at risk for avoidable morbidity and mortality. Under-replacing hydrocortisone can lead to potentially fatal adrenal crises, whereas over-replacing hydrocortisone can lead to Cushing's-like symptoms.[12] Clinical judgement is needed to ensure that corticosteroid regimens ensure that patients' appetite and energy levels are regulated correctly, and dose timing is a key factor in this process.[13] It is possible therefore that this nonadherence to both the dose
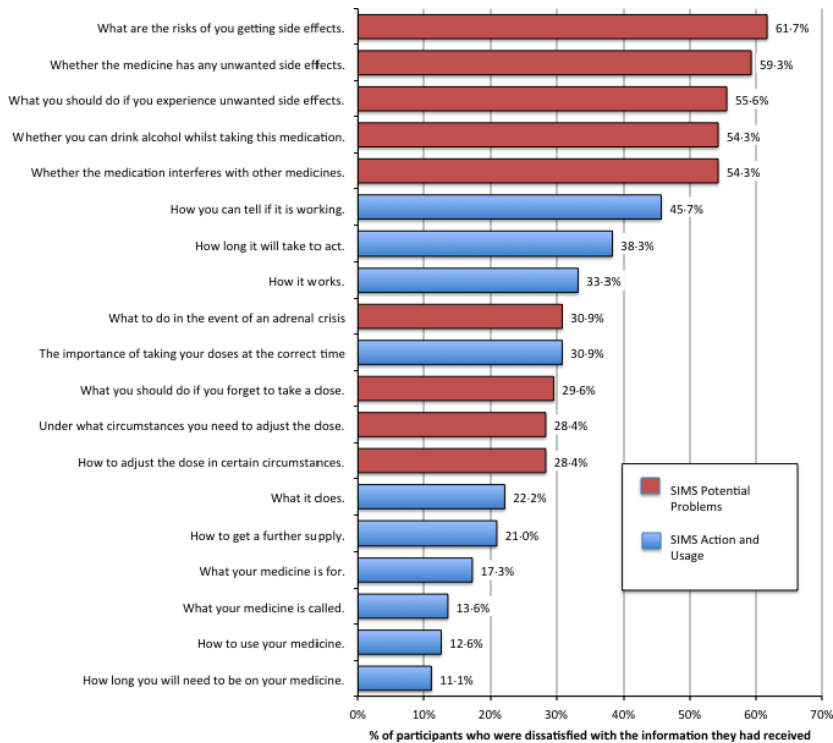
Fig. 4 Dissatisfaction with information about glucocorticoid therapy (GC) on the Satisfaction with Information about Medicines Scale (SIMS). Participants who stated that they had received 'too much', 'too little' or 'none received' were classed as dissatisfied.
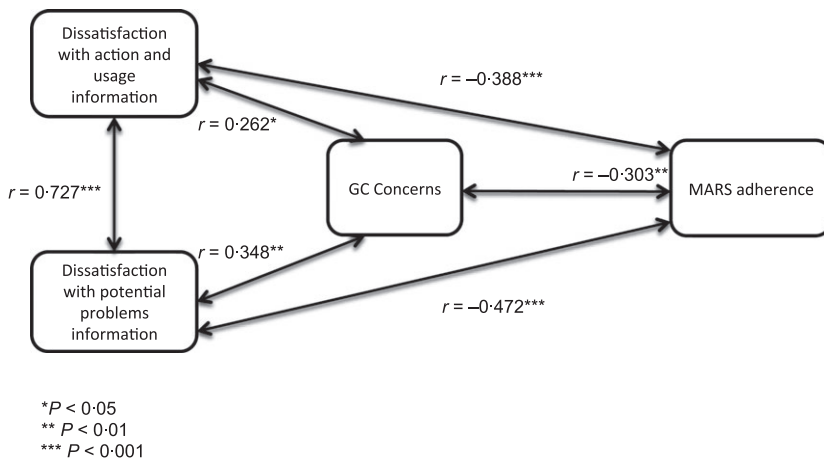

*P < 0·05
** P < 0·01
*** P < 0·001

Fig. 5 Correlation between concerns about medication, satisfaction of information about medicines and adherence.

and timing of GC may increase the impact of AI, leading to weight gain and fatigue.

Glucocorticoid therapy necessity scores were high (mean 4·61 of 5), indicating participants were convinced GC was important for ensuring their current and future health. Most participants reported significant concerns about GC including weight gain, osteoporosis, potential long-term adverse effects and risk of adrenal crisis, which were all reported by more than 50% of participants. These high concerns are similar to those reported in other patients taking GC.[14] In line with the predictions of the Necessity-Concerns Framework,[7,9,15] our findings suggest that even adherent patients may be worried about their GC, and that for some patients, these concerns lead to nonadherence.

Dissatisfaction with information provided about GC adverse effects appeared to be particularly common in our sample, with

participants reporting dissatisfaction with, on average, more than three aspects of information about potential problems with their medication. Participants who were more dissatisfied with the amount of information they had received about their GC had higher concerns and reported more nonadherence. Given the cross-sectional nature of the study, it is not possible to identify cause and effect relationships. However, it is likely that dissatisfaction with information about side effects and concerns might be mutually reinforcing, such that a lack of information about side effects may represent a missed opportunity to reassure patients and alleviate their concerns, while patients who have high concerns may tend to be more dissatisfied with the current standard of information.

Some demographic and clinical factors were associated with nonadherence in out sample. Younger participants, women and

people who were prescribed more than two doses per day of GC were at the highest risk for nonadherence. These findings are difficult to interpret given our small sample size, cross-sectional design and the number of potential uncontrolled confounding factors, and need further investigation. However, they do suggest that for some patients, simplifying their medication regimen may support adherence. There were no significant differences between participants with primary and secondary AI, possibly because the treatment regimens are similar; however, again it is difficult to draw strong conclusions about this finding.

The current study has several limitations. The sample size was too small to detect moderate–small associations between variables or investigate heterogeneity or small subgroups within the sample. We used patient support groups and social media to advertise the survey, and so do not know what proportion of people who saw the survey advertisements responded, potentially meaning that our sample was biased towards people who were interested in issues around their medication. As the survey was cross-sectional, caution is needed before concluding there are causal relationships between the factors. As a self-report study, there may be differences between patients' actual behaviour or, for example, the information they had received, and those that they have reported in this study. Available objective adherence measures, for example electronic monitoring,[16] pharmacy refill records,[17] and pill count,[18] could not be used to validate reported adherence because of the online survey nature of this study.

Despite these limitations, this is, to our knowledge, the first study to evaluate adherence, perceptions of GC and perceptions of GC information using validated measures in AI. Our results show that AI patients have a diverse range of views on their GC. Understanding reasons behind nonadherence and effective medicines use is important for clinicians in helping patient s with long-term conditions effectively self-manage. This study indicates that concerns about potential adverse effects from GC use are very important for patients with AI and influence medicines usage. Strategies to facilitate optimal adherence to GC should support both dosage adherence and timing adherence and should be tailored to the needs of the individual addressing their specific concerns and information needs.

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Author contributions

RH conceived and designed the study and drafted the manuscript. SC analysed the data and drafted the manuscript. SL contributed to study design and drafted the manuscript. PC contributed to study design and drafted the manuscript.

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