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ORIGINAL INVESTIGATION

# A randomised placebo-controlled trial of oral hydrocortisone for treating tobacco withdrawal symptoms

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**Abstract**
*Rationale* Many smokers experience a decline in cortisol to sub-normal levels during the first days of smoking cessation. A greater decline in cortisol is associated with more intense cigarette withdrawal symptoms, urge to smoke and relapse to smoking. Findings from an uncontrolled study suggest that glucocorticoids could ameliorate cigarette withdrawal.
*Objectives* We investigated whether taking oral hydrocortisone would reduce withdrawal symptoms and the desire to smoke on the first day of temporary smoking abstinence compared with placebo.
*Methods* Using a double-blind within-subject randomised crossover design, 48 smokers took a single dose of 40 mg hydrocortisone, 20 mg hydrocortisone or placebo following overnight smoking abstinence. Abstinence was maintained through the afternoon, and withdrawal symptoms and the desire to smoke were rated across the morning. Salivary cortisol was assessed in the afternoon prior to abstinence (baseline) and while abstinent after each treatment.
*Results* There was a significant dose–response relation between dose of hydrocortisone and reduction in depression and anxiety ratings while abstinent, but there were no other statistically significant associations with dose. Overall, the decline in cortisol following smoking cessation (placebo only) was not significant. Cortisol level on the afternoon of smoking abstinence was not significantly associated with symptom ratings.
*Conclusions* Supplements of hydrocortisone do not reduce the desire to smoke but may ameliorate withdrawal-related depression and anxiety, although the clinical benefit is slight.

**Keywords** Smoking · Nicotine · Tobacco · Cortisol · Withdrawal · Craving · Randomised controlled trial

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## Introduction

Tobacco withdrawal symptoms and cravings for cigarettes predict smoking relapse (Killen and Fortmann 1997; Swan et al. 1996; West et al. 1989) and are a serious discomfort to those attempting to stop smoking (Hughes 2006). Little is known about the physiological markers of tobacco withdrawal. Recent research suggests that cortisol may be one such marker. Cortisol is a glucocorticoid which modulates central nervous system activity during stress, and its production has been linked to the ability to cope with stress demands (Biondi and Picardi 1999). Cigarettes stimulate cortisol release and therefore smokers tend to have much higher cortisol levels than non-smokers (Steptoe and Ussher 2006). Two studies have reported no significant

change in cortisol during the first days of smoking abstinence (Benowitz et al. 1984; Pickworth et al. 1996), and one study reported a significant increase in cortisol at this time (Hughes et al. 1988); however, these studies were all limited by including only 10 participants. Several more adequately powered studies have shown that during the first days of smoking cessation, on average, cortisol levels have been found to reduce by up to two thirds, to sub-normal levels (al'Absi et al. 2004; Pomerleau et al. 1992, 2000, Teneggi et al. 2002; Ussher et al. 2006a). This phenomenon may be due to a temporary disruption of the feedback mechanism that controls cortisol levels (al'Absi et al. 2003; Benowitz et al. 1984).

Most attempts to quit smoking fail on the first days of abstinence (Hughes et al. 2004). Low levels of cortisol on the first day of smoking abstinence are associated with higher levels of the urge to smoke, tobacco withdrawal symptoms and perceived stress (Steptoe and Ussher 2006). Although medication such as nicotine replacement therapy (NRT) can mitigate tobacco withdrawal (West and Shiffman 2001), cortisol levels fall to sub-normal levels even in people using NRT at conventional doses (Steptoe and Ussher 2006; Ussher et al. 2006a). One study has found that a greater decline in cortisol following abstinence predicts smoking relapse at 1 week (al'Absi et al. 2004), although another study found no relationship between this decline in cortisol and relapse (Ussher et al. 2006a). The mechanism underlying the observed relationship between a decline in cortisol and increased smoking relapse and withdrawal is unclear. It is possible that low levels of cortisol lead to low mood and craving for cigarettes due to reduced mesolimbic dopamine levels (Reuter and Hennig 2003).

We hypothesised that an intervention which restores sub-normal levels of cortisol on the first day of smoking abstinence would reduce the desire to smoke and cigarette withdrawal symptoms. Findings from an uncontrolled study suggest that glucocorticoids could reduce the intensity of cigarette withdrawal (Bourne 1985), but there are no published randomised trials. We conducted a study to examine whether giving oral hydrocortisone (synthetic cortisol), on the first day of temporary smoking abstinence, significantly reduces tobacco withdrawal symptoms and the desire to smoke, relative to a placebo. We used two doses of hydrocortisone (40 and 20 mg) and hypothesised that there would be a dose–response effect on withdrawal symptoms and the desire to smoke. The trial involved a within-subject design with temporarily abstinent participants, which is commonly used to screen behavioural and pharmacological interventions for smoking cessation (Ussher et al. 2001, West et al. 1999; West and Shiffman 2001).

## Methods

### Study participants

Eligible participants were smokers aged 18 to 65 years, smoking ≥10 cigarettes a day for at least 3 years, smoking their first cigarette within 30 min of waking and having an expired carbon monoxide (CO) reading ≥10 ppm. Exclusion criteria were planning to quit smoking during the next month, receiving psychiatric treatment, having a history of severe depression, receiving oestrogen therapy, night-shift workers, taking corticosteroids or having cautions for corticosteroids (British National Formulary 2010). Participants were recruited in south west London using posters and advertisements in local newspapers. The study took place in St George's, University of London. Participants provided written informed consent and the local ethics committee gave its approval. Individuals completing the study were paid £100.

### Design and procedures

A nurse screened all volunteers via the telephone. Cautions for using corticosteroids were further checked with each volunteer's physician, with consent from the volunteer. Participants attended the laboratory in the late afternoon for baseline assessments. Smoking status was confirmed with an expired CO level (Smokerlyzer, Bedfont Scientific Ltd, UK) of ≥10 ppm. A pre-smoking abstinence saliva sample was provided for cortisol. Cortisol levels in a spot sample taken in the late afternoon correlate strongly with a more complete estimate of diurnal cortisol activity (Edwards et al. 2001).

In this placebo-controlled double-blind crossover study, participants completed three treatment periods (40 mg hydrocortisone, 20 mg hydrocortisone and placebo) in a randomised order. Oral hydrocortisone (Merck Sharp & Dohme Ltd., UK) was administered in doses consistent with standard treatment guidelines for cortisol deficiency (British National Formulary 2010). Using oral hydrocortisone, peak blood concentrations are attained in approximately 1 h and the plasma half-life is approximately 100 min (Medicines and Healthcare Products Regulatory Agency 2007). The hydrocortisone and placebo (lactose) were in capsule form and identical in appearance. They were pre-packed in bottles and consecutively numbered for each person according to the randomisation schedule. Each individual was assigned an order number and received the capsules in the corresponding pre-packed bottle. Drug packaging and randomisation was completed by an independent company (Nova Laboratories Ltd, UK). Independent pharmacists dispensed active or placebo capsules according to a computer-generated randomisation list, using simple randomisation.

The day following laboratory baseline assessments, participants rated their desire to smoke and withdrawal symptoms at 2, 4 and 6 h after waking. This provided a baseline/pre-smoking abstinence assessment of symptoms. Participants then underwent a period of temporary abstinence from smoking. They were instructed not to smoke, or use nicotine products, from 11 pm until after attending an assessment the following afternoon. Previous studies show that, among relatively heavy smokers, 12 to 15 h of temporary smoking abstinence is sufficient to induce significant cravings and withdrawal symptoms (Ussher et al. 2001, 2006b; West et al. 2006). They received a telephone reminder to abstain from smoking. Following overnight abstinence, participants were instructed to take the treatment capsule on waking, so as to mimic the normal morning rise in cortisol (Pruessner et al. 1999). They then rated the desire to smoke and withdrawal symptoms 2, 4 and 6 h after taking the treatment. Following a washout period of 3 to 5 days, during which participants smoked as usual, the above procedure (i.e. overnight smoking abstinence, treatment on waking and ratings of symptoms) was repeated for the remaining two treatments.

## Measures

Demographic and smoking characteristics, including the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al. 1991) and expired CO were measured at the baseline assessment. Although people receiving psychiatric treatment were excluded, some participants might have undiagnosed depression and depression has been associated with hypercortisolism (Carroll et al. 2007); therefore, the Beck Depression Inventory (BDI) was administered (Beck et al. 1988). Overnight smoking abstinence was confirmed by an expired CO reading of <8 ppm.

To determine salivary cortisol, participants inserted a cotton roll in their mouth for a timed period of 2 min and returned the roll to a salivette (Sarstedt, Germany). For the pre-smoking abstinence measure of salivary cortisol, to minimize any acute effects of smoking on cortisol, participants were required to abstain from smoking for at least 30 min before the samples (Reuter et al. 2002). They were instructed not to drink alcohol or take vigorous exercise on the day until after the samples had been taken, or to eat or drink (except water) for 30 min before the visit. Before assay, the saliva samples were stored at −20°C. Samples were thawed and then spun at 3,500 rpm for 10 min to recover the saliva. Cortisol concentration was determined by an enzyme-linked immunoassay developed specifically for the determination of cortisol in saliva (Salimetrics LLC). Assay reliability met the manufacturer's specifications.

Subjective withdrawal symptoms and the desire to smoke were assessed using a variant of the Mood and Physical Symptoms Scale (MPSS, West and Russell 1985), which has good psychometric properties (West and Hajek 2004; West and Ussher 2010; West et al. 2006). The standard withdrawal symptoms assessed were irritability, depression, hunger, anxiety, restlessness and poor concentration. For example, 'How irritable do you feel right now?' (1 = not at all, 4 = somewhat, 7 = extremely). An item on the desire to smoke was added ('How strong is your desire to smoke right now?') which has been used before in laboratory studies on craving (Ussher et al. 2001, 2006b; West et al. 1999). Additionally, due to the relationship between cortisol and stress, the MPSS was used to assess symptoms of tension and stress. Participants were given a palm-top computer (Palm, Tungsten E2) to record their ratings and to receive prompts of when to make ratings. Compliance with electronic assessment tends to be higher than for paper-based assessment (Stone et al. 2003).

## Statistical analysis and sample size

The primary outcome was the desire to smoke during the morning of administration of the treatments, while controlling for pre-smoking abstinence desire to smoke. Secondary outcomes were the desire to smoke and withdrawal symptoms following the treatments. Using the desire to smoke as the primary outcome, it was estimated that a sample size of 50 completing the study would be sufficient to detect a difference of 0.4 standard deviations (SDs) of the difference between the hydrocortisone and placebo treatment scores at 80% power and a significance level of 5%. As there were no prior data, it was not possible to determine the SD of the difference between the two treatment scores; however, existing data suggested that the SD of the raw scores for the desire to smoke would be approximately 1.5 (Ussher et al. 2001, 2006b; West et al. 2006) and the SD of the difference between paired treatment scores would be expected to be less than this. Therefore, the study had the power to detect a difference in symptom scores of 0.6.

Cortisol data were strongly positively skewed; therefore, logarithmic transformations were used. Repeated measures analysis of variance (ANOVA) and paired *t* tests were used to examine differences in log cortisol levels between pre-smoking abstinence and after each of the three treatments. There is evidence from one study that the decline in cortisol on the first day of smoking cessation is more pronounced for men than women (Dušková et al. 2010) and another study found the reverse effect (al'Absi et al. 2004). Therefore, on an exploratory basis, we examined the change in cortisol between pre-smoking abstinence and

following placebo by gender. Change in cortisol between these two points was normally distributed, and therefore, transformation was not needed for this analysis.

For the main analysis, for the desire to smoke and for each withdrawal symptom, the mean of the three scores (i.e. at 2, 4 and 6 h after waking and taking treatment) was calculated. These mean scores were then compared between treatments (placebo, 20 mg hydrocortisone, 40 mg hydrocortisone) adjusting for the pre-smoking abstinence score (mean of 2, 4 and 6 h after waking), using a within-subjects regression model. As the hydrocortisone treatment is intended for those experiencing a drop in cortisol following smoking cessation, the main analysis was repeated adjusting for whether a reduction in post-smoking cessation cortisol was observed during the placebo condition. Also, on an exploratory basis, we repeated this analysis adjusting for gender and for 'intention to quit smoking in the immediate future'. In addition, the main analysis was performed separately for each of the three time points (2, 4 and 6 h after waking) to confirm that the use of a mean score was not suppressing any time-specific effects. We also calculated the actual time intervals between the ratings (i.e. as recorded by the palm-top computers) and compared these between treatments using ANOVA.

To confirm previous reports (Steptoe and Ussher 2006; Ussher et al. 2006a), for the placebo condition only, correlations were used to assess whether lower cortisol on the afternoon of smoking abstinence is associated with increased scores for the desire to smoke and withdrawal symptoms (using mean of ratings 2, 4 and 6 h after taking placebo). STATA version 10 and SPSS version 16 were used for the analysis. The $p$ value was set at 0.05, unless stated otherwise.

## Results

Four hundred and thirty volunteers were assessed for eligibility between November 2007 and November 2008, with 197 ineligible and 169 declining to participate. Sixty-four volunteers were randomised into the trial, eight withdrew from the study, eight were withdrawn for non-compliance and 48 (75%) completed the study. Data on these 48 only were analysed. A CONSORT flow diagram and checklist can be accessed online as supplementary material.

Following each overnight abstinence from smoking, all those retained in the analysis were confirmed as having expired CO readings of <8 ppm. Table 1 presents the baseline characteristics. There were no significant differences between those completing the study and those failing to complete for gender, age or FTND score. No participants reported adverse events.

### Cortisol outcomes

Hydrocortisone is synthetic cortisol; therefore, hydrocortisone supplementation would be expected to increase cortisol levels, and this was investigated. For all saliva samples, participants confirmed that they had not taken alcohol or vigorous exercise that day and had not eaten or drunk (except water) for 30 min before the sample. Cortisol was strongly positively skewed; therefore, logarithmic transformations were used. There was no evidence for a significant 'order effect' (i.e. cortisol results differing according to whether the treatment was the first, second or third received), nor was the order/treatment interaction significant. An overall repeated measures ANOVA comparing afternoon cortisol during pre-smoking abstinence and following the three treatments was significant ($F$=5.9, $p$=0.001, $n$=42, six participants each had a missing cortisol sample due to insufficient saliva). Paired $t$ tests revealed no significant difference between cortisol at pre-abstinence, after the placebo treatment or after the 20 mg hydrocortisone treatment (see Table 2). There was a significant increase in cortisol levels after 40 mg hydrocortisone compared with pre-abstinence, placebo and 20 mg hydrocortisone.

To confirm previous reports that most smokers experience a decline in cortisol on the first day of smoking abstinence, we examined the numbers experiencing a decline versus an increase in cortisol levels between pre-smoking abstinence and the afternoon of the placebo condition. For 48% (22/46) of participants, cortisol levels decreased on the afternoon of abstinence following placebo (mean (SD) decrease=6.4 (9.8) nmol/l, median=3.3, interquartile range (IQR)=1.7–5.4), while for 52% (24/46) cortisol increased (mean (SD) increase=5.2 (8.1) nmol/l, median=1.9, IQR=0.9–6.6). Overall there was no significant change in cortisol following smoking cessation (mean (SD) change=−0.3 (10.6) nmol/l, $p$=0.83). The change in cortisol following smoking cessation was significantly different for females versus males ($t$=3.1, $p$=0.004). For females, there was an average increase in cortisol (mean (SD)=3.4 (9.3) nmol/l) and for males there was an average decline in cortisol (mean (SD)=6.0 (10.8) nmol/l).

For two individuals, the depression scores (BDI) at baseline were classed as moderate depression (scores of 21 and 22). However, there was no evidence of hypercortisolism among these individuals and they showed the expected cortisol response to the treatments; therefore, they were retained in the analysis.

When assessing the placebo condition only, neither cortisol concentration on the afternoon of smoking abstinence, nor the change in cortisol between pre and post-abstinence, were significantly correlated with scores for the change in desire to smoke and withdrawal symptoms between pre and post- abstinence ($n$=46). These correla-

**Table 1** Baseline characteristics ($N$=48)

| Characteristics | |
|---|---|
| Age (range 18–60 years) | 38.4 (11.5)[a] |
| Full-time education (10 to 25 years) | 13.9 (3.2)[a] |
| FTND score (2 to 9) | 5.6 (1.7)[a] |
| Smoking rate, cigarettes a day (10 to 40) | 19.3 (6.3)[a] |
| Salivary cortisol level (nmol/l) (2.7 to 41.7) | 10.2 (8.3)[a] |
| CO (ppm) pre-smoking abstinence (10 to 28) | 15.3 (4.4)[a] |
| BDI score (0 to 22) | 5.5 (5.7)[a] |
| Female | 33 (69)[b] |
| Caucasian | 41 (85)[b] |
| Managerial/professional occupation | 16 (33)[b] |
| Married/living with partner | 12 (25)[b] |
| Intends quitting smoking in the immediate future (but not in the next month[c]) | 22 (46)[b] |

*FTND* Fagerström Test for Nicotine Dependence, *CO* expired carbon monoxide level, *ppm* particles per million, *BDI* Beck Depression Inventory

[a] Mean (SD)

[b] Number (%)

[c] Those intending to quit in the next month were screened out as being ineligible

tions remained non-significant when conducting a separate analysis for males and females.

## Outcomes for withdrawal symptoms and the desire to smoke

For the main analysis scores for the desire to smoke and for each of the seven withdrawal symptoms (mean of scores 2, 4 and 6 h after taking treatment, see Table 3) were compared between the three treatments, adjusting for pre-smoking abstinence scores (Table 4). For most comparisons there was a significant 'order effect' ($p$=0.019 to 0.049), with ratings being higher for the first period of treatment compared with the second and third periods, but the order/treatment interactions were not significant. Therefore, all analyses were adjusted only for order of treatment. Compliance with the instruction to complete ratings every 2 h after waking was high both for pre-abstinence and following each treatment (mean (SD) time interval (minutes) between ratings for all time points combined (i.e. 2, 4 and 6 h after waking): pre-abstinence=122.3 (7.1), placebo=121.4 (11.0), 20 mg=121.4 (8.7), 40 mg=120.5 (8.3)) and there were no significant differences in mean time intervals between treatments. For two symptoms, ratings between the treatments were significantly different, and for three symptoms, the findings approached significance. Specifically, there was a significant trend for lower scores for depression and anxiety with higher doses of hydrocortisone. In addition, scores for hunger, poor concentration and tension tended to be lower for hydrocortisone versus placebo, with the findings approaching significance ($p$=0.056 to 0.086). The effect of hydrocortisone on withdrawal symptoms and the desire to smoke did not differ significantly between participants who showed a decline in cortisol following smoking cessation and those who did not experience this decline. The effect of the treatments on symptoms did not differ significantly by gender, although a trend was noted for greater reduction in

**Table 2** Comparison of afternoon cortisol levels at pre-smoking abstinence and following each treatment (during smoking abstinence) (only includes those with data for all four measures, $n$=42)

| | | Ratio of geometric means (95% CIs) | | |
|---|---|---|---|---|
| | | $p$ values for $t$ tests, using logarithmic transformed data | | |
| | Geometric mean (nmol/l) | Versus pre-abstinence | Versus placebo | Versus 20 mg HC |
| Pre-abstinence | 8.4 | | | |
| Placebo | 8.5 | 1.0 (0.8 to 1.3)<br>$p$=0.885 | | |
| 20 mg HC | 7.4 | 1.1 (0.9 to 1.5)<br>$p$=0.347 | 1.1 (0.8 to 1.6)<br>$p$=0.475 | |
| 40 mg HC | 13.3 | 1.6 (1.2 to 2.2)<br>$p$=0.005* | 1.6 (1.2 to 2.1)<br>$p$=0.005* | 1.8 (1.3 to 2.5)<br>$p$=0.001* |

*HC* oral hydrocortisone, *CI* confidence interval

*$p$<0.008 indicates statistical significance (adjusted for multiple testing)

**Table 3** Mean (SD) ratings of withdrawal symptoms and the desire to smoke (mean of three ratings at 2, 4 and 6 h after waking/taking treatment, score ranges from 1 to 7) at pre-smoking abstinence and following smoking abstinence for each treatment ($n$=48)

| Withdrawal/desire to smoke item | Pre-smoking abstinence | Placebo | 20 mg HC | 40 mg HC |
|---|---|---|---|---|
| Desire to smoke | 3.8 (1.1) | 4.6 (1.4) | 4.4 (1.3) | 4.5 (1.5) |
| Irritability | 2.6 (1.3) | 3.7 (1.6) | 3.4 (1.4) | 3.6 (1.3) |
| Depression | 1.9 (1.0) | 2.9 (1.3) | 2.6 (1.1) | 2.3 (1.0) |
| Hunger | 2.7 (1.1) | 3.2 (0.9) | 3.1 (1.0) | 3.0 (1.2) |
| Anxiety | 2.4 (1.2) | 3.4 (1.5) | 3.0 (1.2) | 3.0 (1.2) |
| Restlessness | 2.5 (1.2) | 3.5(1.4) | 3.4 (1.2) | 3.4 (1.2) |
| Poor concentration | 2.7 (1.3) | 3.5 (1.3) | 3.2 (1.2) | 3.3 (1.4) |
| Tension | 2.6 (1.4) | 3.5 (1.4) | 3.2 (1.3) | 3.3 (1.2) |
| Stress | 2.6 (1.4) | 3.4 (1.5) | 3.2 (1.3) | 3.3 (1.3) |

*HC* oral hydrocortisone

withdrawal symptoms for men than for women. Nor did the effect of treatments on symptoms differs according to the intention to quit smoking. A comparison of scores separately for each of the three time points (2, 4 and 6 h after waking) confirmed that the use of mean scores was not suppressing any time-specific effects of treatment.

## Discussion

This is the first randomised placebo-controlled trial to assess whether hydrocortisone supplementation alleviates smoking withdrawal phenomena. We found that hydrocortisone had no effect on the primary outcome, the desire to smoke, on the first day of smoking abstinence. There was some evidence for effects on secondary outcomes, with two of eight mood symptoms showing significant reductions in intensity with hydrocortisone, and three others showing near significant decreases. Contrary to expectations, around half the participants showed a rise in cortisol on smoking abstinence, but there was no evidence that the effect of hydrocortisone on the primary and secondary outcomes was modified significantly by whether participants' cortisol rose or fell.

This study has important strengths, the chief of which is that it is the first placebo-controlled trial of hydrocortisone supplementation for treating smoking withdrawal. A previous uncontrolled study suggested hydrocortisone was efficacious (Bourne 1985), but it is impossible to exclude bias, confounding, or placebo effects, which this design does. We also used a within-subject design, improving the precision of our estimates of treatment effects (Perkins et al. 2006). Nevertheless, there were limitations. First, we noted an order effect in that the first period of abstinence was associated with higher withdrawal; an effect we mitigated by control in the analysis. Second, unlike several previous studies (al'Absi et al. 2004; Pomerleau et al. 1992, 2000; Teneggi et al. 2002; Ussher et al. 2006a), there was no overall significant reduction in cortisol levels following abstinence. As around half of the participants experienced an increase in cortisol on abstinence and half experienced a decrease in cortisol, it is possible that this change in cortisol

**Table 4** Comparison of ratings for the desire to smoke and withdrawal symptoms following smoking abstinence between treatments ($n$=48) (adjusted for order of treatment and pre-smoking abstinence ratings of symptoms)

| Withdrawal/desire to smoke | 20 mg HC versus placebo | | 40 mg HC versus placebo | | 40 mg HC versus 20 mg HC | | $p$ for trend |
|---|---|---|---|---|---|---|---|
| | $B$[a] | $p$ | $B$[a] | $p$ | $B$[a] | $p$ | |
| Desire to smoke | −0.16 | 0.46 | −0.08 | 0.73 | 0.08 | 0.611 | 0.729 |
| Irritability | −0.26 | 0.158 | −0.06 | 0.80 | 0.21 | 0.189 | 0.795 |
| Depression | −0.25 | 0.102 | *−0.60* | *<0.001* | *−0.34* | *0.010* | *<0.001* |
| Hunger | −0.17 | 0.120 | −0.27 | 0.086 | −0.11 | 0.495 | 0.086 |
| Anxiety | *−0.38* | *0.024* | *−0.45* | *0.011* | −0.07 | 0.589 | *0.011* |
| Restlessness | −0.14 | 0.394 | −0.03 | 0.864 | 0.11 | 0.471 | 0.864 |
| Poor concentration | −0.32 | 0.056 | −0.19 | 0.347 | 0.13 | 0.352 | 0.345 |
| Tension | −0.32 | 0.062 | −0.22 | 0.228 | 0.10 | 0.449 | 0.224 |
| Stress | −0.22 | 0.200 | −0.16 | 0.370 | 0.05 | 0.702 | 0.367 |

*HC* oral hydrocortisone

[a] $B$ represents the average increase or decrease in withdrawal score (range of scores=1 to 7) for the given treatment versus its comparator, adjusted for order of treatment and pre-smoking abstinence rating. Italicized text indicates comparisons that are significantly different at $p<0.05$

occurs by chance. Some previous studies have reported no overall significant change in cortisol following smoking abstinence (Benowitz et al. 1984; Pickworth et al. 1996) and another study reported a significant increase in cortisol at this time (Hughes et al. 1988); however; these studies were all limited by small sample sizes ($n$=10).

Our hypothesis was that hydrocortisone supplementation would 'correct' the fall in cortisol and ameliorate withdrawal phenomena. That half the participants experienced no fall reduced the power of the study to detect this effect. Furthermore, there was neither a significant effect, nor a suggestion of enhanced effect of hydrocortisone supplementation on withdrawal, in those showing a fall in cortisol on abstinence.

There was no evidence for gender significantly modifying the effect of treatment on withdrawal symptoms. However, there was a tendency (non-significant) for greater reductions in withdrawal symptoms for men and specifically for men who had previously shown a drop in cortisol post-abstinence. These putative findings would need to be further researched as this study was not powered to identify differential effects by gender. In addition, we observed a significantly greater decline in cortisol following smoking cessation for men versus women. This finding is consistent with that of Dušková et al. (2010), but another study (Ussher et al. 2006a) did not find any gender difference and a third study found a greater reduction in cortisol for women versus men (al'Absi et al. 2004). Our finding also conflicts with the evidence that men do not have more difficulty quitting smoking than women (Killen et al. 2002; Velicer et al. 2007) and may have less difficulty (Bjornson et al. 1995; Cepeda-Benito et al. 2004; Piper et al. 2010; Wetter et al. 1999). Further work is needed to determine whether the gender difference found here is reliable and to consider whether it relates to evidence that men have higher cortisol response to acute psychological stress compared with women (Kudielka and Kirschbaum 2005).

In contrast to previous findings (Ussher et al. 2006a), we found no evidence for lower cortisol on the first morning of smoking abstinence being significantly correlated with the desire to smoke or withdrawal symptoms. The difference in findings could be explained by differences in the design of the two studies. First, the previous study recruited smokers undergoing a quit attempt, whereas participants in the present study underwent temporary abstinence. Requiring only temporary abstinence is an approach commonly used to screen behavioural and pharmacological interventions for smoking cessation (Ussher et al. 2001; West et al. 1999; West and Shiffman 2001), and the present study and previous studies using this approach have observed similar increases in smoking withdrawal and the desire to smoke as found among those trying to quit, when using the same measures (e.g. Ussher et al. 2003; West and Willis 1998). However, it is possible that the previously observed associations between low cortisol, withdrawal symptoms and relapse are partly a psychological phenomenon related to a quit attempt. This observation also lessens the importance of the finding that cortisol levels increased in about half of abstinent smokers, as again this may be due to the sample only undergoing temporary abstinence, although several previous studies have observed a significant decline in cortisol on the first day of temporary smoking abstinence (Teneggi et al. 2002; Pomerleau et al. 1992, 2000). Using participants involved in a quit attempt is not possible in a crossover study of this kind. To increase the clinical relevance of the sample, one solution might be to exclusively recruit smokers intending to quit (in the present study around half of the participants said they were intending to quit in the immediate future, although not in the next month, as this would have made them ineligible, see Table 1), although the intention to quit did not appear to influence the effects of the treatments on withdrawal symptoms. Also, a possible disadvantage of focusing on those intending to quit is that some participants may not comply with the protocol through attempting to use temporary abstinence as a 'springboard' for a quit attempt, as has been found in previous studies requiring temporary abstinence (e.g. Ussher et al. 2001, 2006b). A second methodological difference is that in the previous study cortisol levels on the first afternoon of smoking abstinence were correlated with the desire to smoke and withdrawal symptoms across the first week of abstinence; whereas in the present study, afternoon cortisol on the first day of abstinence was related to symptoms across the morning preceding the cortisol assessment. Studies are needed to establish whether low cortisol on the first day of a quit attempt reliably predicts the subsequent desire to smoke and withdrawal symptoms.

We found no effects of hydrocortisone on the desire to smoke but the effects were evident for depression and anxiety and we now examine the cause and consequence of these effects. Depressed mood is associated with a lower likelihood of smoking cessation and two antidepressants, bupropion and nortriptyline, have been shown to be effective in enhancing cessation (Hughes et al. 2007). Selective serotonin uptake inhibitors are effective antidepressants (Cipriani et al. 2010) but are ineffective in improving smoking abstinence rates when used as aids to cessation (Hughes et al. 2007). They do, however, ameliorate the adverse mood changes and other mood-related changes occurring after cessation (Covey et al. 2002). Other evidence suggests that the key withdrawal phenomenon causing the return to smoking is the strength of the desire to smoke (Killen and Fortmann 1997; Swan et al. 1996; West et al. 1989), and failure of hydrocortisone to influence the desire to smoke is an important negative

finding. It is also noteworthy that the observed effects of hydrocortisone on mood symptoms were not modified significantly by whether participants' cortisol rose or fell following abstinence. This finding perhaps suggests that the effect of hydrocortisone on depression and anxiety is due to the general effects of steroids in enhancing mood (Plihal et al. 1996), but it might indicate that steroids have a role in mood changes after cessation. If the latter is true, it could be that steroids would be effective in ameliorating post-cessation depression and anxiety. Depression develops in up to 1 in 10 smokers after cessation and the incidence is perhaps twice this in people with a past history of depression (Hughes 2007). Clinical trials of hydrocortisone in post-cessation depression would be needed to examine this. In severe mood disturbance, clinicians could choose to use small to moderate doses of hydrocortisone and for short-term use as this has few adverse side effects (British National Formulary 2010).

In summary, this placebo-controlled trial showed no short-term effects of hydrocortisone on withdrawal phenomena, except those that could be explained by non-specific mood-enhancing effects of steroids. We found that, overall, cortisol did not fall on the first day of temporary smoking abstinence and was not related to the primary outcome of the desire to smoke, the variable with the most clinical relevance. The latter findings are inconsistent with some of the previous studies recruiting smokers involved in an attempt to quit smoking and the present study requires replication among those making a quit attempt.

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The protocol for this study is available by contacting the first author.

**Trial registration** The effect of hydrocortisone on the desire to smoke and tobacco withdrawal symptoms' (http://www.controlled-trials.com/ISRCTN81211851/)

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