Appendix D Effectiveness evidence

Agha, 2004

Bibliographic Reference	Agha, A.; Liew, A.; Finucane, F.; Baker, L.; O'Kelly, P.; Tormey, W.; Thompson, C. J.; Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency; Clinical Endocrinology; 2004; vol. 60 (no. 6); 688-93

Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Ireland
Study setting	Department of Endocrinology, Beaumont Hospital, Ireland
Study dates	Not reported
Sources of funding	Unclear "We would like to thank Professor Dermot Kenny and the staff of the RCSI Clinical Research Centre, Dublin, Ireland where the study was conducted. We are indebted to Dr Jamie Zadeh of Charing Cross Hospital, London, UK who performed the CBG assays. Dr Agha was in receipt of a Pharmacia International Research Fellowship."
Inclusion criteria	Male adult hypopituitary patients with partial ACTH deficiency, defined as a fasting 08·00 h total serum cortisol exceeding 200 nmol/l with a stimulated peak value of less than 500 nmol/l, ACTH reserves were assessed fewer than 6 months before the start of the study in all patients. Because glucagon stimulation is associated with subnormal cortisol responses in about 8% of healthy subjects (Rao & Spathis, 1987), patients whose ACTH deficiency was defined by abnormal response to GST were only included if they also had both significant GH deficiency (stimulated peak < 3 ng/ml and IGF-1 below age-specified reference range) and gonadotrophin deficiency, in order to exclude those with false negative responses to glucagon.
Exclusion criteria	Patients with severe cardiac or respiratory disease

	patients with terminal illness Patients on antiepileptic therapy or other medications which interfere with hydrocortisone metabolism. Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) level
Recruitment / selection of participants	"Identified from the Beaumont Hospital Pituitary Database" "We identified 14 patients who fulfilled the criteria,10 agreed to participate"
Intervention(s)	Conventional full-dose hydrocortisone - 10mg twice daily for 1 week Half dose hydrocortisone - 5mg twice daily for 1 week
Population subgroups	None
Comparator	No hydrocortisone treatment for 1 week Note: not a placebo
Number of participants	10
Duration of follow-up	3 weeks total - 1 week per treatment crossover
Additional comments	Analysis of variance (anova) models were used to compare serum cortisol results of patients on full-dose, half-dose and no hydrocortisone treatments, and controls at various time periods and also to compare peak and trough cortisol values between patients and controls. Multiple comparison tests using a Bonferroni correction factor was used to determine if results reach significance at the 5% level. The Student's t-test was used to compare body mass index (BMI), PR, BP, plasma sodium and CBG levels between patients and control groups. P-values less than 0·05 were taken as significant.

Study arms

No treatment (N = 10)

5mg hydrocortisone twice daily for 1 week (N = 10)

10mg hydrocortisone twice daily for 1 week (N = 10)

Characteristics

Study-level characteristics

Characteristic	Study (N = 10)
% Female No of events	n = 0 ; % = 0
Mean age (SD) Mean (SD)	43.9 (10.8)
BMI (kg/m²)	31.1 (4.5)

Characteristic	Study (N = 10)
Mean (SD)	

Outcomes

Study timepoints

1 week

Clinical parameters and cortisol

Outcome	No treatment, 1 week, N = 10	5mg hydrocortisone twice daily for 1 week, 1 week, N = 10	10mg hydrocortisone twice daily for 1 week, 1 week, N = 10
Peak cortisol (nmol/L) Mean (SD)	323 (74.2)	424.4 (93.9)	508.6 (86)
Trough cortisol (nmol/L) Mean (SD)	180.5 (64.1)	165.6 (71.7)	149.8 (49.1)
Pulse rate (beats per minute) Mean (SD)	67.9 (2.4)	66.6 (3.1)	68.2 (3.4)
Systolic blood pressure (mmHg) Mean (SD)	131.1 (9.6)	134.3 (14.5)	129.5 (12.4)
Diastolic blood pressure (mmHg) Mean (SD)	79.1 (11.6)	83.7 (10.7)	83.4 (8.7)
Plasma sodium (mmol/L) Mean (SD)	141.2 (2.2)	140.2 (1.7)	140.5 (1.7)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

Cortisol levels

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Partially applicable

Pulse rate

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Blood pressure

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Plasma sodium

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Behan, 2016

Bibliographic Reference	Behan, L. A.; Carmody, D.; Rogers, B.; Hannon, M. J.; Davenport, C.; Tormey, W.; Smith, D.; Thompson, C. J.; Stanton, A.; Agha, A.; Low-dose hydrocortisone replacement is associated with improved arterial stiffness index and blood pressure dynamics in severely adrenocorticotrophin-deficient hypopituitary male patients; European Journal of Endocrinology; 2016; vol. 174 (no. 6); 791-9

Study details

Secondary publication of another included study- see primary study for details	Behan 2011
Other publications associated with this study included in review	Behan 2011 [Optimizing glucocorticoid replacement therapy in severely adrenocorticotropin-deficient hypopituitary male patients]
Trial name / registration number	Irish Medicines Board Clinical Trial Number–CT900/459/1 EudraCT Number–2007-005018-37 [Same as Behan 2011]
Study type	Randomised controlled trial (RCT)

Study location	RCSI Clinical Research Centre, Dublin, Ireland
Study setting	Clinic
Study dates	Not stated
Sources of funding	An unrestricted educational grant from Pfizer Endocrine Care
Inclusion criteria	[Same as Behan 2011] Adults Known severe ACTH deficiency defined by a fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak cortisol in response to insulin-induced hypoglycaemia of <400 nmol/l
Exclusion criteria	Aged less than 18 years, Patients with acute medical or surgical illness, patients with advanced cardiac/pulmonary disease, patients with a terminal illness, patients on glucocorticoids for purposes other than ACTH deficiency and those on agents that interfere with corticosteroid metabolism. Female patients [excluded because of the unpredictable effects of oestrogen status on corticosteroid binding globulin (CBG) levels and thus total cortisol concentration and also free cortisol kinetics]
Recruitment / selection of participants	Not stated
Intervention(s)	Hydrocortisone oral: Dose A (20 mg 0800 h, 10 mg 1600 h), Dose B (10 mg 0800 h and 1600 h) Dose C (10 mg 0800 h and 5 mg 1600 h) 6 weeks of each dose regimen
Population subgroups	N/A
Comparator	See "Intervention(s)"
Number of participants	n=10 intervention, n=10 control
Duration of follow-up	6 weeks for each treatment arm
Indirectness	N/A
Additional comments	Not stated, likely ITT

Study arms

Dose A [20 mg 0800 h, 10 mg 1600 h] (N = 10)

Dose B [10 mg 0800 h and 1600 h] (N = 10)

Dose C [10 mg 0800 h and 5 mg 1600 h (N = 10)

Control (N = 10)

Healthy matched controls

Outcomes

24h Ambulatory Blood Pressure levels

Outcome	Dose A [20 mg 0800 h, 10 mg 1600 h], , N = 10	Dose B [10 mg 0800 h and 1600 h], , N = 10	Dose C [10 mg 0800 h and 5 mg 1600 h, , N = 10	Control, , N = 10
24h systolic BP (mmHg) Mean (SD)	115 (12)	117 (12)	115 (13)	121 (10)
24h diastolic BP Mean (SD)	70 (8)	68 (8)	68 (7)	73 (8)

At the end of each 6-week treatment regimen, schedule patients were admitted for 28 h to the clinical research centre to undergo metabolic investigations, which included a 24-h ambulatory BP measurement (24-h ABPM). On each admission, between 0730 and 0800 h, patients were fitted with validated oscillometric devices to record 24-h ambulatory blood pressure (SpaceLabs 90202 or 90207), programmed to obtain BP readings at 30-min intervals for 24 h throughout each 28-h admission period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

24h Ambulatory BP

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

Behan, 2011

Bibliographic Reference	Behan, L. A.; Rogers, B.; Hannon, M. J.; O'Kelly, P.; Tormey, W.; Smith, D.; Thompson, C. J.; Agha, A.; Optimizing glucocorticoid replacement therapy in

severely adrenocorticotropin-deficient hypopituitary male patients; Clinical Endocrinology; 2011; vol. 75 (no. 4); 505-13

Study details

Other publications associated with this study included in review	Behan 2016 [Low-dose hydrocortisone replacement is associated with improved arterial stiffness index and blood pressure dynamics in severely adrenocorticotrophin-deficient hypopituitary male patients]
Trial name / registration number	Irish Medicines Board Clinical Trial Number–CT900/459/1 EudraCT Number–2007-005018-37 [Same as Behan 2016]
Study type	Randomised controlled trial (RCT)
Study location	RCSI Clinical Research Centre, Dublin, Ireland
Study setting	Clinic
Study dates	Not stated
Sources of funding	An unrestricted educational grant from Pfizer Endocrine Care and Sanofi Aventis Pharmaceuticals
Inclusion criteria	Adults Known severe ACTH deficiency defined by a fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak cortisol in response to insulin-induced hypoglycaemia of <400 nmol/L
Exclusion criteria	Aged less than 18 years, Patients with acute medical or surgical illness, patients with advanced cardiac/pulmonary disease, patients with a terminal illness, patients on glucocorticoids for purposes other than ACTH deficiency and those on agents that interfere with corticosteroid metabolism. Female patients [excluded because of the unpredictable effects of oestrogen status on corticosteroid binding globulin (CBG) levels and thus total cortisol concentration and also free cortisol kinetics]
Recruitment / selection of participants	Not stated
Intervention(s)	Hydrocortisone oral: Dose A (20 mg 0800 h, 10 mg 1600 h), Dose B (10 mg 0800 h and 1600 h) Dose C (10 mg 0800 h and 5 mg 1600 h)

	6 weeks of each dose regimen
Population subgroups	N/A
Comparator	See Intervention(s)
Number of participants	n=10 intervention, n=10 control
Duration of follow-up	6 weeks for each treatment arm
Indirectness	N/A
Additional comments	Not stated, likely ITT

Study arms

Dose A (20 mg 0800 h, 10 mg 1600 h) (N = 10)

Dose B (10 mg 0800 h and 1600 h) (N = 10)

Dose C (10 mg 0800 h and 5 mg 1600 h) (N = 10)

Control (N = 10)

Healthy matched controls

Characteristics

Study-level characteristics

Characteristic	**Study (N = 10)**
% Female Nominal	0
Mean age (SD) Mean (SD)	46 (15)
BMI (kg/m2) Mean (SD)	29.8 (5.3)
Basal cortisol (nmol/L) Mean (SD)	76.8 (6.5)
Basal testosterone (pmol/L) Mean (SD)	14.2 (4.1)

Outcomes

Raw quality of life scores

Outcome	Dose A (20 mg 0800 h, 10 mg 1600 h), , N = 10	Dose B (10 mg 0800 h and 1600 h), , N = 10	Dose C (10 mg 0800 h and 5 mg 1600 h), , N = 10	Control, , N = 10
SF-36 physical functioning Mean (SD)	88.5 (18.4)	79.5 (24)	80.5 (24.5)	92.9 (13.4)
SF-36 Role Physical Mean (SD)	77.5 (38)	62.5 (35.8)	55 (45.3)	95.8 (12)
SF-36 bodily pain Mean (SD)	85.1 (20)	82.5 (23.8)	76.5 (22.8)	81 (21.2)
SF-36 general health Mean (SD)	62.8 (18.6)	61.8 (13)	59.8 (15)	77 (12.7)
SF-36 vitality Mean (SD)	62.5 (24.9)	47.5 (23.3)	44 (24.5)	70 (13.3)
SF-36 social functioning Mean (SD)	90 (17.4)	92.5 (13.4)	85 (18.4)	91 (14.5)
SF-36 Role Emotional Mean (SD)	83.3 (36)	66.6 (41.5)	73.3 (40.9)	91.6 (20.2)
SF-36 Mental Health Mean (SD)	79.6 (17.8)	80 (18.9)	80 (17.4)	78.8 (13.1)
NHP Energy level Mean (SD)	36.3 (43.6)	35.1 (42.5)	41.3 (37.3)	3.2 (11.1)
NHP Pain Mean (SD)	8.1 (22.2)	7 (15.6)	10.6 (21.6)	2.1 (4.4)
NHP Emotional reaction Mean (SD)	8.5 (10.3)	7.3 (15.5)	8.6 (17.1)	8.9 (13.4)
NHP Sleep Mean (SD)	20.7 (23.2)	15.3 (30.4)	10.9 (17.7)	11.2 (18.4)

Outcome	Dose A (20 mg 0800 h, 10 mg 1600 h), , N = 10	Dose B (10 mg 0800 h and 1600 h), , N = 10	Dose C (10 mg 0800 h and 5 mg 1600 h), , N = 10	Control, , N = 10
NHP Social Isolation Mean (SD)	8.5 (20.6)	7.5 (13.3)	0 (0)	4.4 (13.6)
NHP Physical abilities Mean (SD)	8.9 (15.5)	13.1 (21.8)	14.4 (20.5)	2.2 (5.6)

- SF-36 physical functioning - Polarity - Higher values are better.
- SF-36 Role Physical - Polarity - Higher values are better.
- SF-36 bodily pain - Polarity - Higher values are better.
- SF-36 general health - Polarity - Higher values are better.
- SF-36 vitality - Polarity - Higher values are better.
- SF-36 social functioning - Polarity - Higher values are better.
- SF-36 Role Emotional - Polarity - Higher values are better.
- SF-36 Mental Health - Polarity - Higher values are better.
- NHP Energy level - Polarity - Lower values are better.
- NHP Pain - Polarity - Lower values are better.
- NHP Emotional reaction - Polarity - Lower values are better.
- NHP Sleep - Polarity - Lower values are better.
- NHP Social Isolation - Polarity - Lower values are better.
- NHP Physical abilities - Polarity - Lower values are better.
- Following 6 weeks of each regimen patients underwent 24 h serum cortisol sampling and QoL assessment with the Short Form 36 (SF36) and the Nottingham Health Profile (NHP) questionnaires.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

SF-36 scores.

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Very serious risk of bias as details on recruitment, randomisation, and blinding not provided)*
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

NHP Scores

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Very serious risk of bias as details on recruitment, randomisation, and blinding not provided)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

Benson, 2012

Bibliographic Reference	Benson, S.; Neumann, P.; Unger, N.; Schedlowski, M.; Mann, K.; Elsenbruch, S.; Petersenn, S.; Effects of standard glucocorticoid replacement therapies on subjective well-being: a randomized, double-blind, crossover study in patients with secondary adrenal insufficiency; European Journal of Endocrinology; 2012; vol. 167 (no. 5); 679-85

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	None
Trial name / registration number	No trial registration reported. "The study was approved by the Local Ethics Committee (permit no. 03-2279)"
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	University Hospital of Essen, Germany
Study dates	Not reported
Sources of funding	"This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector."
Inclusion criteria	Inclusion criteria were age 18–75 years and stable substitution therapy of all pituitary axes (if necessary) for at least 3 months.
Exclusion criteria	Patients were excluded if Beck Depression Inventory score exceeded the cutoff indicating moderate-to-severe depressive symptoms. Pregnancy and a previous history of hypercortisolism also led to exclusion from the study. A peak cortisol of more than 500 nmol/l during the insulin tolerance test was used to categorize the patients as adrenal sufficient (patient controls (PC)) and a peak cortisol of <450 nmol/l to diagnose SAI. Owing to difficulties in establishing a clear diagnosis, patients with peak cortisol levels between 450 and 500 nmol/l were excluded from the study.

Recruitment / selection of participants	Medical records from n=248 patients who had undergone pituitary surgery at the University Hospital of Essen, Germany, and evaluation of the adrenal function within the previous 12 months were screened Ninety-three patients met all inclusion criteria, of those 43 (n=23 SAI, n=20 PC) agreed to participate. Three SAI patients dropped out after initial consent but before treatment, and two SAI patients were excluded during the study for noncompliance, resulting in 18 SAI patients and 20 PC that completed the study protocol.
Intervention(s)	three different established glucocorticoid replacement therapies (i.e., treatment A, hydrocortisone 10 mg-placebo-5 mg-placebo; treatment B, hydrocortisone 10 mg-5 mg-placebo-5 mg; and treatment C, prednisone 5 mg-placebo-placebo-placebo) for 4-week periods. Identically looking capsules containing either medication or placebo were prepared by the pharmacy of the University Hospital Essen. Capsules were designed to be completely resolved within 30 min; hence, an effect of capsules on the pharmacokinetics of the active drugs can be excluded. Capsules were administered at distinct time points (i.e., 0700, 1200, 1500, and 1800 h). Given that a wash out period is not feasible in adrenal insufficient patients, questionnaires were completed at the end of each 4-week treatment regimen.
Population subgroups	None
Comparator	See intervention - 3 different treatment regimes
Number of participants	18
Duration of follow-up	12 weeks total - 4 weeks per treatment crossover
Indirectness	
Additional comments	Effects of replacement regimens on psychological parameters within SAI patients were assessed with repeated measures analysis of covariance (ANCOVA) controlling for disease duration. In case of significant ANCOVA treatment effects, post hoc paired t-tests were computed. For variables that were measured over the course of the study days (i.e., current well-being and alertness), two-way ANCOVAs with the repeated factors replacement treatment and time were computed.

Study arms

Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks (N = 18)

Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks (N = 18)

Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks (N = 18)

Excluded in protocol as prednisone not used in UK - included for info only.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 18)**
% Female No of events	n = 10; % = 55.6
Mean age (SD) Mean (SD)	52 (10.3)
BMI (kg/m²) Mean (SD)	27 (7.4)

Outcomes

Study timepoints

- 4 weeks

HRQoL, emotional distress, alertness

Outcome	**Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks, 4-week, N = 18**	**Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks, 4-week, N = 18**	**Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks, 4-week, N = 18**
SF-36 physical sum scale Mean (SD)	43.9 (10.5)	40.7 (13.4)	42.8 (12.2)
SF36 psychological sum scale Mean (SD)	46.3 (7.7)	46.4 (12.8)	46.5 (12.7)
BSI Global symptom severity Mean (SD)	57.9 (11.4)	58.1 (12.9)	58.2 (13.5)

Outcome	Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks, 4-week, N = 18	Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks, 4-week, N = 18	Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks, 4-week, N = 18
0700h Mean (SD)	2.5 (0.35)	2.3 (0.32)	2.4 (0.33)
1200h Mean (SD)	1.7 (0.24)	1.7 (0.29)	1.7 (0.19)
1500h Mean (SD)	1.8 (0.27)	1.8 (0.24)	2 (0.39)
1800h Mean (SD)	1.7 (0.21)	2.1 (0.3)	1.8 (0.27)
2200 Mean (SD)	2.7 (0.39)	3.4 (0.5)	3.3 (0.48)
Satisfaction with medication (100mm visual analog scale) Mean (SD)	51.2 (33.1)	56.6 (27.3)	62.1 (28.5)

- SF-36 physical sum scale - Polarity - Higher values are better.
- SF36 psychological sum scale - Polarity - Higher values are better.
- BSI Global symptom severity - Polarity - Lower values are better.
- Stanford Sleepiness Scale - Polarity - Lower values are better.
- Satisfaction with medication (100mm visual analogue scale) - Polarity - Higher values are better.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

SF-36 Score

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BSI Global Symptom Severity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Stanford Sleepiness Scale

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Satisfaction with medication

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Isidori, 2018

Bibliographic Reference	Isidori, A. M.; Venneri, M. A.; Graziadio, C.; Simeoli, C.; Fiore, D.; Hasenmajer, V.; Sbardella, E.; Gianfrilli, D.; Pozza, C.; Pasqualetti, P.; Morrone, S.; Santoni, A.; Naro, F.; Colao, A.; Pivonello, R.; Lenzi, A.; Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial; The Lancet Diabetes & Endocrinology; 2018; vol. 6 (no. 3); 173-185

Study details

Trial name / registration number	NCT02277587
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Academic hospital
Study dates	March 1, 2014, to June 30, 2016
Sources of funding	Italian Ministry of University and Research No pharma sponsor. "The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."
Inclusion criteria	Eligible patients were aged 18–80 years, had primary or secondary adrenal insufficiency, were taking conventional glucocorticoid therapy (hydrocortisone or cortisone two or three times a day plus daily doses of fludrocortisone as needed), had been stable for at least 3 months before enrolment, and were willing to change their regimen according to random allocation.
Exclusion criteria	Not specified
Recruitment / selection of participants	Methods not specified
Intervention(s)	Once-daily modified-release hydrocortisone tablet. Patients allocated to once daily, modified-release hydrocortisone were instructed to take the dose on waking, before

	leaving their bed. Patients previously on multiple doses of hydrocortisone a day received the same total daily dose, whereas patients previously on cortisone received 0·8 mg of hydrocortisone per 1 mg of cortisone, as recommended by the European Medicines Agency drug fact sheet.
Population subgroups	• Primary AI (n=44) • Secondary AI (n=45) • Female (n=47) • Male (n=42)
Comparator	Standard glucocorticoid therapy. Patients assigned to continue standard therapy were instructed to take the first dose on waking before leaving their bed and subsequent doses according to their established schedule (two or three times a day), but with the last dose no later than 1700 h.
Number of participants	n= 89
Duration of follow-up	24 weeks
Indirectness	No concerns
Additional comments	Efficacy analyses included data from all patients who had received at least one dose of study drug. Authors assessed normality of distribution for all interventions at all timepoints using the Shapiro-Wilk's test (p>0·05). Log transformation or reciprocal transformation was used to correct for skewed data and a mixed-model analysis to assess changes in outcomes with accommodation for repeated measurements. In the mixed-model analysis, the patient was a random effect and treatment, time, and treatment-by-time interaction were fixed effects. The differences in change from baseline to week 12 and week 24 were analysed between the groups using an ANCOVA model that included baseline outcome as a covariate and treatment as a fixed effect and used the last observation- carried-forward principle.

Study arms

MR-HC (N = 46)

Standard glucocorticoid (N = 43)

Characteristics

Arm-level characteristics

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
Female No of events	n = 25; % = 54	n = 22; % = 51
Primary AI No of events	n = 22; % = 48	n = 22; % = 51
Secondary AI No of events	n = 24; % = 52	n = 21; % = 49
Other autoimmune disorder No of events	n = 12; % = 26	n = 12; % = 28

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
Pituitary tumor or surgery No of events	n = 22; % = 48	n = 20; % = 47
Other hypothalmic-pituitary failure No of events	n = 2; % = 4	n = 1; % = 2
Adrenalectomy No of events	n = 2; % = 4	n = 2; % = 5
Use of hydrocortisone at baseline No of events	n = 20; % = 43	n = 17; % = 40
Use of cortisone at baseline No of events	n = 26; % = 57	n = 26; % = 60
Baseline HC equivalent dose Mean (95% CI)	16 (14 to 18)	18 (15 to 21)
Diabetes No of events	n = 8; % = 17	n = 7; % = 16
BMI (kg/m2) Mean (95% CI)	27 (25 to 28)	26 (24 to 27)
Bodyweight (kg) Mean (95% CI)	75 (69 to 81)	70 (63 to 76)
Fasting blood glucose (mg/dL) Mean (95% CI)	89 (80 to 98)	79 (74 to 84)
Insulin (mU/ml) Mean (95% CI)	10 (8 to 12)	9 (7 to 12)
Total cholesterol (mg/dL) Mean (95% CI)	-1 (-11 to 10)	0 (-9 to 9)
HBA1C (%) Mean (95% CI)	5.2 (4.9 to 5.4)	5.5 (5.2 to 5.8)
Age Mean (95% CI)	48 (43 to 52)	49 (44 to 54)
Duration of adrenal insufficiency (Months) Median (IQR)	42 (24 to 108)	48 (24 to 132)
Fludrocortisone No of events	n = 21; % = 46	n = 20; % = 47

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
AddiQoL Mean (95% CI)	82 (78 to 86)	83 (76 to 89)

Outcomes

Difference from baseline at 24 weeks

Outcome	MR-HC, , N = 43	Standard glucocorticoid, , N = 35
BMI (kg/m2) Mean (95% CI)	-0.9 (-1.7 to -0.1)	0.7 (-0.1 to 1.5)
Bodyweight (kg) Mean (95% CI)	-2.1 (-4 to -0.3)	1.9 (-0.1 to 3.9)
Fasting blood glucose (mg/dL) Mean (95% CI)	7 (3 to 10)	5 (0 to 11)
Insulin (mU/ml) Mean (95% CI)	0 (-2 to 2)	0 (-3 to 3)
Total cholesterol (mg/dL) Mean (95% CI)	-1 (-11 to 10)	0 (-9 to 9)
HbA1c (%) Mean (95% CI)	-0.2 (-0.3 to -0.1)	0.1 (0 to 0.2)
AddiQoL Total score, Addison's disease specific QoL Mean (95% CI)	7 (4 to 10)	2 (-1 to 5)
Flu or flu-like events in 6 mos Mean (95% CI)	-1.2 (-1.7 to -0.7)	-0.4 (-0.9 to 0.2)

Anthropometric measures [BMI, bodyweight] adjusted for age, sex, type of adrenal insufficiency, diabetes mellitus, smoking, and outcome at baseline. All other outcomes [HbA1c, fasting blood glucose, insulin, total cholesterol, flu-like events, AddiQoL] adjusted for age, sex, BMI, type of adrenal insufficiency, diabetes, smoking, and outcome at baseline.

Treatment-related difference at 24 weeks

Outcome	MR-HC vs Standard glucocorticoid, , N2 = 43, N1 = 35
BMI (kg/m2) Mean (95% CI)	-1.7 (-3 to -0.5)
BMI (kg/m2) Mean (p value)	-1.7 (0.008)
Bodyweight (kg) Mean (95% CI)	-4 (-6.9 to -1.1)

Outcome	MR-HC vs Standard glucocorticoid, , N2 = 43, N1 = 35
Bodyweight (kg) Mean (p value)	-4 (0.008)
HbA1c (%) Mean (95% CI)	-0.3 (-0.5 to -0.1)
HbA1c (%) Mean (p value)	-0.3 (0.001)
Fasting blood glucose (mg/dL) Mean (95% CI)	3 (-2 to 9)
Fasting blood glucose (mg/dL) Mean (p value)	3 (0.24)
Insulin (mU/ml) Mean (95% CI)	0 (-4 to 4)
Insulin (mU/ml) Mean (p value)	0 (0.99)
Total cholesterol (mg/dL) Mean (95% CI)	0 (-16 to 15)
Total cholesterol (mg/dL) Mean (p value)	0 (0.96)
AddiQoL Mean (95% CI)	5 (1 to 9)
AddiQoL Mean (p value)	5 (0.027)
Flu or flu-like events in 6 mos Mean (95% CI)	-1 (-1.6 to -0.4)
Flu or flu-like events in 6 mos Mean (p value)	-1.7 (0.0002)

Anthropometric measures [BMI, bodyweight] adjusted for age, sex, type of adrenal insufficiency, diabetes mellitus, smoking, and outcome at baseline. All other outcomes [HbA1c, fasting blood glucose, insulin, total cholesterol, flu-like events, AddiQol] adjusted for age, sex, BMI, type of adrenal insufficiency, diabetes, smoking, and outcome at baseline.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BMI

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

AddiQoL

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups. Also, risk of measurement bias in patient-reported outcomes.)*
Overall bias and Directness	Overall Directness	Directly applicable

Bodyweight

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*
Overall bias and Directness	Overall Directness	Directly applicable

HbA1c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*
Overall bias and Directness	Overall Directness	Directly applicable

Illness

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Werumeus Buning, 2015

Bibliographic Reference	Werumeus Buning, J.; Brummelman, P.; Koerts, J.; Dullaart, R. P.; van den Berg, G.; van der Klauw, M. M.; Tucha, O.; Wolffenbuttel, B. H.; van Beek, A. P.; The effects of two different doses of hydrocortisone on cognition in patients with secondary adrenal insufficiency--results from a randomized controlled trial; Psychoneuroendocrinology; 2015; vol. 55; 36-47

Study details

Secondary publication of another included study- see primary study for details	This is the primary report for trial registration NCT01546922
Other publications associated with this study included in review	Primary report for trial registration NCT01546922 Further outcomes reported in: Buning (2016) Effects of hydrocortisone on the regulation of blood pressure: results from a randomized controlled trial Buning (2016) Hydrocortisone dose influences pain, depressive symptoms and perceived health and adrenal insufficiency: a randomized controlled trial
Trial name / registration number	NCT01546922
Study type	Randomised controlled trial (RCT) "Randomized double-blind cross-over study" "Patients were randomly assigned to either group 1 or group 2 by the research pharmacy with a block size of 4."
Study location	Netherlands
Study setting	"Patients were recruited for participation at the endocrine outpatient clinic of the University Medical Center Groningen (UMCG), a tertiary referral center for pituitary surgery in the Netherlands."
Study dates	"All patients were tested in the period between May 2012 and June 2013."
Sources of funding	"This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector."
Inclusion criteria	All patients had SAI for which they received GC substitution therapy.

	To avoid effects of switching to a different type of GCs, all patients on CA were converted to treatment with HC in a bioequivalent dose (i.e., CA dose (in mg) times 0.8 when compared to HC dose (mg)) during a four-week run-in phase. The diagnosis of SAI was based on internationally accepted biochemical criteria, principally early morning (0800—0900 h) serum cortisol measurements and, if necessary, an insulin tolerance test. Early morning cut-off cortisol levels for adrenal insufficiency in our center were validated for patients with hypothalamic—pituitary disorders as previously published (Dullaart et al., 1999). Thyroid hormone deficiency was based on a low serum free thyroxine concentration (<11.0 pmol/l). Growth hormone (GH) deficiency was based on a low insulin-like growth factor 1 (IGF-1) Z-score (less than 2 SD) and/or an insufficient peak GH concentration (<10 mU/l) in response to insulin-induced hypoglycaemia or a peak growth hormone <18 mU/l during an arginine-GHRH test. Insufficiency of the pituitary—gonadal axis was defined in men as a testosterone concentration below 10 nmol/l, in premenopausal women (aged < 50 years) as loss of menses and in postmenopausal women (aged > 50 years) as LH and FSH concentrations below 15 mU/l. Diabetes insipidus was defined as the incapacity to properly concentrate urine (increased urine volume with low urine osmolality) in the face of a high plasma osmolality (and sodium) and/or current treatment with desmopressin. Biochemical control of adequacy of hormonal substitution treatment was judged by the physicians that were responsible for the care of the participating patients using free thyroxine, IGF-1 and testosterone levels where necessary. Other inclusion criteria were age 18—75 years, body weight of 50—100 kg at screening, time interval of at least one year between study entry and tumor treatment with surgery and/or radiotherapy, and adequate replacement of all other pituitary hormone deficiencies for at least six months prior to entry of the study.
Exclusion criteria	Main exclusion criteria were inability of legal consent, documented major cognitive impairment (MMSE < 24) (Lezak et al., 2004), drug abuse or dependence, current psychiatric disorders, treatment for a malignancy, shift work, previous Cushing's disease, hospital admission during the study, diabetes mellitus with medication known to be able to induce hypoglycemia (e.g., sulfonylurea derivatives and insulin) and a history of frequent episodes of clinical hypocortisolism. The concomitant use of other corticosteroids and drugs known to interfere with HC metabolism, e.g., anti-epileptics, was not allowed either.
Recruitment / selection of participants	In this randomized double-blind cross-over study, patients were recruited for participation at the endocrine outpatient clinic of the University Medical Center Groningen (UMCG), a tertiary referral center for pituitary surgery in the Netherlands. A total of 63 patients were included in this study, of whom 60 patients completed the run-in phase and the baseline measurement (mean (SD) age, 52 (13), range 19—73, 35 males, 25 females).
Intervention(s)	Group 1 first received a physiological low dose of HC for 10 weeks, followed by a physiological high dose for another 10 weeks. Group 2 first received a physiological high dose for 10 weeks, followed by a physiological low dose. Patients were treated with oral tablets containing either 5 mg HC (low dose) or 10 mg HC (high dose). Only the research pharmacy knew which dose was administered in each period. In the low dose condition, patients received a cumulative daily dose of 0.2-0.3 mg HC per kg body weight in three divided doses (before breakfast, before lunch, before diner). In the high dose condition, patients received the double amount, 0.4-0.6 mg HC per kg body weight. In cases of intercurrent illness or fever, patients were allowed to double or triple their HC dose. Because the study aimed to investigate two different dosing schemes, increasing the dose of HC was allowed for a maximum of 7 days (i.e., 10% of the study time and of the cumulative HC dose) but not in the week preceding the second

	and the third visit. Compliance with the study medication was assessed in several ways. Firstly, by patient reports in daily diaries: patients were instructed to daily report if they had forgotten and/or doubled their medication and if so, how many doses they had forgotten or doubled. Secondly, the tablets returned by the patients after each study period were counted. Lastly, cortisol concentrations in plasma between the two study periods were compared.
Population subgroups	None reported
Comparator	See intervention - High v Low dose HC
Number of participants	47 included in analyses. (63 randomised - 60 completed run-in phase - 60 started first 10-week treatment period, 53 completed - 53 started second 10-week treatment period, 47 completed)
Duration of follow-up	20 weeks overall - 10 weeks per treatment
Indirectness	NA
Additional comments	Because of the absence of relevant data from literature, we performed a power analysis. A study with 2 arms, each with 25 patients (total number of patients of 50) is able to detect an effect size of 0.4 (two-sided alpha = 0.05 and beta = 0.80) in test results even when between test correlations are poor (0.50). An effect size of 0.4 was chosen because it was considered a relevant change with a small to medium size effect. To allow for a drop-out rate of ±20% a total number of ±60 patients were needed. Cognitive performance data were presented as mean Z-score (SD). Higher Z-scores represent better cognitive performance compared to healthy subject of the same age, sex and educational level. Normality of data was analyzed using Q—Q plots. Since not all data were normally distributed, non-parametric tests for paired samples were used. To compare the cognitive performances at baseline of group 1 and group 2, the Mann—Whitney U-test was used. The cognitive performance which was obtained while on a low dose of HC was compared to the performance on cognitive tests while on a high dose of HC by using the Wilcoxon Signed Rank Test. In addition, Cohen's d effect sizes were calculated to give a measure of the magnitude of the difference. An effect size of d = 0.2 is considered a small effect, d = 0.5 a moderate effect and d = 0.8 a large effect.

Study arms

Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

Characteristics

Study-level characteristics

Characteristic	Study (N = 47)
% Female Sample size	n = 18; % = 38.3
Mean age (SD) Median (IQR)	55 (43 to 61)

Characteristic	Study (N = 47)
BMI (kg/m²) Median (IQR)	26.6 (24.5 to 29.4)

Outcomes

Study timepoints

10 week

Comparison of impaired scores between the low dose and high dose hydrocortisone

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Immediate memory No of events	n = 13; % = 27.7	n = 15; % = 31.9
Short-term memory No of events	n = 3; % = 6.4	n = 4; % = 8.5
Delayed memory No of events	n = 8; % = 17	n = 8; % = 17
Recognition No of events	n = 6; % = 12.8	n = 3; % = 6.4
Divided attention errors No of events	n = 6; % = 12.8	n = 7; % = 14.9
Visual scanning errors No of events	n = 5; % = 10.6	n = 5; % = 10.6
Fluency No of events	n = 10; % = 21.3	n = 10; % = 21.3
Working memory No of events	n = 3; % = 6.4	n = 4; % = 8.5
Cognitive flexibility No of events	n = 6; % = 12.8	n = 6; % = 12.8
Social cognition (Number of patients showing impaired score) No of events	n = 18; % = 38.3	n = 11; % = 23.4

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Psychomotor speed (Number of patients showing impaired score) No of events	n = 17; % = 36.2	n = 24; % = 51.1

Data also available for all tests as mean Z scores in Table 4 of article.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

Memory test

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Attention scores.

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Executive function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Werumeus Buning, 2016

Bibliographic Reference	Werumeus Buning, J.; van Faassen, M.; Brummelman, P.; Dullaart, R. P.; van den Berg, G.; van der Klauw, M. M.; Kerstens, M. N.; Stegeman, C. A.; Muller Kobold, A. C.; Kema, I. P.; Wolffenbuttel, B. H.; van Beek, A. P.; Effects of Hydrocortisone on the Regulation of Blood Pressure: Results From a Randomized Controlled Trial; Journal of Clinical Endocrinology & Metabolism; 2016; vol. 101 (no. 10); 3691-3699

Study details

Secondary publication of another included study- see	Primary report: Buning (2015) The effects of two different doses of hydrocortisone on cognition in patients with secondary adrenal insufficiency - results from a randomized controlled trial.

primary study for details	
Other publications associated with this study included in review	Further outcomes: Buning (2016) Hydrocortisone dose influences pain, depressive symptoms and perceived health in adrenal insufficiency: a randomized controlled trial Also: Sorgdrager (2018) Hydrocortisone affects fatigue and physical functioning through metabolism of tryptophan: a randomized controlled trial
Trial name / registration number	NCT01546922
Study type	Randomised controlled trial (RCT)
Study location	See Buning (2015)
Study setting	See Buning (2015)
Study dates	See Buning (2015)
Sources of funding	See Buning (2015)
Inclusion criteria	See Buning (2015)
Exclusion criteria	See Buning (2015)
Recruitment / selection of participants	See Buning (2015)
Intervention(s)	See Buning (2015)
Population subgroups	See Buning (2015)
Comparator	See Buning (2015)
Number of participants	47
Duration of follow-up	20 weeks total - 10 weeks per treatment crossover
Additional comments	Normally distributed data were presented as mean (SD), non-normally distributed data were presented as median [interquartile range], and categorical data were presented as number or percentage. Normality of data was analysed by visual inspection of Q-Q plots and histograms. To test for period and carryover effects, the procedure developed by Altman was used (32). In this procedure, to test for a carryover effect, the average response to both treatments (i.e., of the low dose and high dose combined) was compared between the two treatment groups. If these average responses were not different between the treatment groups, the effect of the treatment was considered the same irrespective of the order in which the treatments were administered (32). All variables were compared using the Wilcoxon signed rank test for paired observations. Statistical significance was set at $P < 0.05$.

Study arms

Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

Outcomes

Study timepoints

10 weeks

Anthropometric measures and biochemical and hormonal analysis

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Systolic blood pressure (mmHg) Mean (SD)	133 (14)	138 (16)
Diastolic blood pressure (mmHg) Mean (SD)	76 (10)	78 (9)
Weight (kg) Standardised Mean (SD)	82.8 (14)	83.3 (14.3)
BMI (kg/m2) Mean (SD)	26.9 (4)	27.1 (4)
Plasma sodium (mmol/L) Median (IQR)	142 (141 to 143)	142 (141 to 143)
Plasma potassium (mmol/L) Median (IQR)	3.9 (3.7 to 4)	3.8 (3.6 to 4)
Plasma creatinine (micromol/L) Median (IQR)	82 (66 to 88)	80 (68 to 89)
Serum corticosteroid binding globulin (CBG) (microg/ml) Median (IQR)	53.2 (49.1 to 63)	56.5 (49 to 62.5)
Plasma renin concentration (pg/mL) Median (IQR)	11.6 (6.7 to 17.3)	8.6 (5.9 to 14.9)

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Serum aldosterone (pmol/L) Median (IQR)	150 (77 to 256)	107 (43 to 235)
Aldosterone to renin ratio (pmol/ng) Median (IQR)	13.8 (7.3 to 21.3)	11 (6.1 to 19.8)
Transtubular potassium gradient Median (IQR)	7.42 (6.12 to 9.48)	7.47 (6 to 9.18)
Plasma copeptin (pmol/L) Median (IQR)	3.7 (2.5 to 5)	3.4 (2.5 to 4.9)
Urine sodium (mmol/24hour) Median (IQR)	142 (119 to 206)	161 (112 to 200)
Urine potassium (mmol/24hour) Median (IQR)	77 (64 to 96)	83 (69 to 103)
Creatinine clearance calculated (ml/min) Mean (SD)	117 (37)	117 (29)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Blood pressure

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

BMI

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Plasma sodium

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable