Health Technology Assessment 2002; Vol. 6: No. 19

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Health Technology Assessment
NHS R&D HTA Programme

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Declared competing interests of the authors: none

Published December 2002

This report should be referenced as follows:

Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al.* Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(19).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/21/02.

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ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

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Contents

List of abbreviations

AGHDA	Assessment of Growth Hormone Deficiency in Adults
AO-GHD	adult-onset growth hormone deficiency
BDI	Beck Depression Inventory
BMD	bone mineral density
BNF	*British National Formulary*
CI	confidence interval
CO-GHD	childhood-onset growth hormone deficiency
CPRS	Comprehensive Psycho-pathological Rating Scale
CSF	chronic fatigue syndrome
DDAVP	1-deamino-8-D-arginine vasopressin
DEC	Development and Evaluation Committee
df	degrees of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSQ	Disease-Specific Questionnaire
GH	growth hormone
GHD	growth hormone deficiency
GHDQ	Growth Hormone Deficiency Questionnaire
GHQ	General Health Questionnaire
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HbA_{1C}	glycosylated haemoglobin
HDS	Hamilton Depression Scale
HSCL	Hopkins Symptom Checklist
IGF-I	insulin-like growth factor I
ITT	insulin tolerance test
KIMS	Pharmacia & Upjohn International Metabolic Database
KSQ	Kellner Symptom Questionnaire
LFS	Life Fulfilment Scale
MeSH	Medical Subject Heading
MFS	Mental Fatigue Scale
MMPI	Minnesota Multiphasic Personality Inventory
MONICA	Multinational MONItoring of Trends and Determinants in CArdiovascular Disease
MPHD	multiple pituitary hormone deficiencies
MRI	magnetic resonance imaging
NA	not applicable
NHP	Nottingham Health Profile
NICE	National Institute for Clinical Excellence
PGWB	Psychological General Well-Being (Schedule)
POMS	Profile of Mood States
QALY	quality-adjusted life-year
QoL	quality of life
QoL-AGHDA	Quality of Life Assessment of Growth Hormone Deficiency in Adults
QUOROM	Quality of Reporting of Meta-analyses
RCT	randomised controlled trial
SADS	Schedule for Affective Disorders and Schizophrenia
SAS	Social Adjustment Scale
SCL-90	Symptom Checklist-90
SD	standard deviation
SE	standard error
SES	Self-Esteem Scale
SMQ	Sjoberg Mood Questionnaire
STAI	State–Trait Anxiety Inventory
VAT	value-added tax
WMD	weighted mean difference

Executive summary

Background

The Society for Endocrinology estimates that the prevalence rate of adults with growth hormone deficiency (GHD) is approximately 2 in 10,000 of the adult population, with adult-onset GHD accounting for approximately 1 in 10,000. This prevalence rate equates to approximately 4200 patients with adult-onset GHD in England and Wales. The incidence rate of adult-onset GHD, based on the incidence of pituitary tumours, is suggested to be 1 per 100,000 annually.

Objectives

This review considers the clinical effectiveness and cost-effectiveness of growth hormone (GH) therapy in adults with either adult-onset or childhood-onset GHD, using impact on quality of life (QoL) as the outcome measure.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

The main electronic databases were searched, with English language limits, for the periods up to May 2001. The journal *Clinical Endocrinology* was handsearched from 1993 to August 2000. Bibliographies of related papers were assessed for relevant studies, and experts were contacted for advice and peer review, as well as to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria, which were applied independently by two reviewers, with any disagreements resolved through discussion.

- Intervention was biosynthetic human GH (somatropin).
- Participants were adults diagnosed with GHD, including those who were continuing GH treatment from childhood.
- Outcomes were QoL measures.
- Designs were systematic reviews of randomised controlled trials (RCTs), or individual RCTs, that assessed the effects of GH compared with placebo. Economic evaluations of somatropin in adults had to include a comparator (or placebo) and assess both the costs and consequences (outcomes).

Data extraction and quality assessment

Data extraction and quality assessment were undertaken independently by two reviewers, with any disagreements resolved through discussion. The quality of RCTs was assessed using the Jadad criteria. The internal validity of economic evaluations was assessed using the *BMJ* checklist, and external validity by a series of relevant questions.

Data synthesis

The clinical effectiveness and cost-effectiveness of GH in adults were synthesised through a narrative review with full tabulation of results of all included studies. Meta-analyses were carried out using Cochrane Review Manager software, if practical and appropriate. For the economic evaluation, a cost model was constructed using the best available evidence to determine costs in a UK setting.

Results

Number and quality of studies

In total, 17 RCTs met the inclusion criteria of the review. These RCTs were of variable quality, with most trials having a Jadad quality score of 2/5 or 3/5. The outcome measure of interest was QoL, which was reported using a variety of measurement scales. These were mostly generic, such as the Nottingham Health Profile (NHP), and Hamilton Depression Scale.

No reliable economic evaluations of GH in adults were found.

Summary of benefits

The evidence suggests that GH may improve QoL, although most change scores were modest and only a few were statistically significant. The interpretation of

these change scores in terms of meaningfulness to patients is difficult. The analysis of the individual dimensions of the NHP from individual trials demonstrated statistically significant improvements in the GH replacement group, compared with the control group, for pain, emotional reactions and sleep. Meta-analysis showed a statistically significant difference in favour of GH on the NHP social isolation dimension.

Costs and cost-effectiveness

GH replacement in adults was found to cost £3424 annually at the average maintenance GH dose. Sensitivity analyses showed that the cost of GH therapy in adults is sensitive to GH dose, cost of GH and length of treatment. Further economic modelling was limited by the lack of a suitable effectiveness measure, and cost per unit of effect or cost per quality-adjusted life-year could not be estimated.

Conclusions

Implications

Fewer than half the adults with GHD are currently receiving GH therapy. Some may not be in clinical need; however, due to variation in prescribing policy, others who could potentially benefit are not being prescribed GH replacement therapy. Extending the use of GH to all those with severe GHD would have a budgetary impact. However, not all patients offered GH replacement therapy are likely to accept treatment.

Trials of GH therapy in adults with GHD have not shown consistent benefit on QoL. GH may have beneficial effects on other factors (such as bone mineral density and cardiac function) that may indirectly affect QoL, but these factors were not examined in this review.

Research recommendations

Further research is needed to develop methods to interpret the meaning of changes in QoL scores, and these methods can then be applied in well-designed trials (e.g. to determine optimal dosing strategies) and economic evaluations.

Chapter 1
Aim and background

Aim of the review

The aim of this report is to provide a systematic review of the clinical effectiveness and cost-effectiveness of growth hormone (GH) in the treatment of adults suffering from GH deficiency (GHD).

The outcome measure considered in this review is quality of life (QoL). There are two reasons for the selection of this outcome measure. Firstly, QoL is of immediate relevance to patients. Although other outcomes, such as bone mineral density (BMD), cardiovascular effects and exercise performance, are important to adults with GHD, they may be of less immediate relevance. Secondly, the greatest immediate indication for GH replacement is in patients who are assessed as having impaired QoL.

Description of underlying health problem

Adult GHD may be of adult onset or childhood onset, and may occur as isolated GHD or as multiple hormone deficiencies. Adult-onset GHD (AO-GHD) is commonly due to pituitary tumours or their treatment, and cranial irradiation, and characteristically presents with the following problems:[1]

- reduced QoL (especially reduced energy levels)
- altered body composition (reduced lean body mass and increased fat mass, especially in the trunk)
- osteopenia/osteoporosis
- dry skin – reduced sweating
- reduced muscle strength and exercise capacity
- lipid abnormalities (especially elevated low-density lipoprotein cholesterol)
- insulin resistance
- increased levels of fibrinogen and plasminogen activator inhibitor
- increased thickness of the intima media
- cardiac dysfunction.

Childhood-onset GHD (CO-GHD) may continue into adulthood. Adolescents with CO-GHD who have been treated with GH and are approaching the completion of therapy for height indications are referred to as transition patients. They have achieved adult or near-adult height, which is commonly defined as a growth rate of less than 2.5 cm/year and a bone age of greater than 17 years in boys and greater than 14 years in girls. They are retested to determine whether they continue to be GH-deficient.

Severe GHD is defined as a peak GH concentration of less than 3 µg/l in response to insulin-induced hypoglycaemia, compared with a response of more than 5 µg/l in most normal individuals.[2] Putative GHD with or without one additional pituitary hormone deficit requires confirmation by two tests of GH status. In AO-GHD, this usually means two GH provocation tests. In CO-GHD, the insulin-like growth factor I (IGF-I) estimation can replace one of the two GH provocation tests.

All patients with severe GHD are eligible for GH replacement, and the goal for replacement in adults is to normalise GH levels and correct the abnormalities associated with adult GHD. The rationale for providing GH replacement therapy in these cases is based on the fact that people with severe GHD have problems such as those listed above. The majority view among UK endocrinologists is that the major indication for offering GH replacement to patients with severe GHD is reduced QoL, and therefore QoL is the outcome measure considered here. In order to assess which adult patients would benefit from GH replacement, patient-perceived impairment of QoL is assessed at clinical interviews.

Incidence and prevalence

The Society for Endocrinology (UK) estimates that the prevalence rate of adults with GHD is approximately 2 in 10,000 of the adult population, with AO-GHD accounting for approximately 1 in 10,000.[1] This prevalence rate equates to approximately 4200 patients with AO-GHD in England and Wales. The incidence rate of AO-GHD, based on the incidence of pituitary tumours, is suggested to be 1 per 100,000 annually.[3]

Current service provision

The clinical management of GHD in adults is centred on the provision of GH replacement therapy. However, there are local variations in practice within the UK. The reasons include a reluctance to fund this treatment on the part of health authorities and certain primary care clinicians, a reluctance of secondary care clinicians to prescribe GH, health authority policies that are age related or based on an arbitrary number of patients prescribed at one time, and other factors such as the expertise within secondary care. A number of health authorities and primary care providers have agreed, however, to fund GH replacement on a shared care arrangement, as set out by the Society for Endocrinology and discussed in *Box 1* (Society for Endocrinology, Bristol, UK: personal communication, 2001).

Shalet[4] reported that "only one fifth to one-quarter of requests for prescription are met". More recently, the Society for Endocrinology estimated that approximately 1750 (38%) adult GH-deficient patients in the UK receive GH replacement therapy (Society for Endocrinology, Bristol, UK: personal communication, 2001). This means that, due to a variety of reasons, some 60% of patients with GHD are not prescribed GH replacement. Some of these patients may have been considered for treatment and were not found to be in clinical need; in other cases, treatment is being declined by the patients. The practice recommendations for the treatment of adults with severe GHD are presented in *Box 1*.

BOX 1 Practice recommendations from the Society for Endocrinology regarding adults with severe GHD

Diagnostic test

- The gold standard test is the insulin tolerance test (ITT), with a serum cut-off of less than 3 μg/l in response to hypoglycaemia, for diagnosis of severe GHD.[1] Other available tests are arginine, acetyl-cholinesterase inhibito pyridostigmine and glucagon tests.
- The presence of at least one of the following clinical features is also used to aid the decision to recommend GH replacement: severely decreased QoL, reduced bone density, reduced exercise tolerance and adverse cardiovascular risk profile, cardiac decompensation, or the patient is already receiving full supplementation of other deficient hormones as required.

Transition patients

- Childhood GHD does not always continue into adulthood. Once children reach their final height, they should be reviewed for GHD.

Adult management

- Responsibilities for the care of the adult patient with GHD are best placed under a shared care arrangement between clinic and primary care.[1]
- The clinic conducts the initial assessment and titrates the dose, undertaking measurement of serum IGF-I, waist–hip ratio, blood pressure, QoL, bone density, thyroid function and serum bio-chemistry, glucose and glycosylated haemoglobin (HbA_{1C}), weight and body mass index, and patient education. Baseline, 6-month and then yearly pituitary imaging is also undertaken in patients known to have a residual pituitary tumour.
- It is recommended that patients are initially placed on a 6-month trial of GH replacement therapy, and if they show improvement based on QoL question-naires, then they should be offered the opportunity to continue therapy on a long-term basis.
- Primary care practices are then asked to continue to prescribe GH and to monitor the patient for adverse effects and carry out measurements of weight, blood pressure, glucose and HbA_{1C} every 3 months and then every 6 months when the patient is stable.

Description of the intervention

Biosynthetic human GH (somatropin) is available as five preparations on the UK market: Genotropin® (Pharmacia Laboratories Ltd, Milton Keynes, UK), Humatrope® (Eli Lilly and Co Ltd, Basingstoke, UK), Norditropin® (Novo Nordisk Ltd, Crawley, UK), Saizen® (Serono Pharmaceuticals Ltd, Feltham, UK) and Zomacton® (Ferring Pharmaceuticals Ltd, Langley, UK). Each product is produced by recombinant DNA technology and has a sequence identical to that of human GH. Recombinant human GH has been available since 1985, shortly after GH from cadaveric human pituitaries was withdrawn from use because of its association with the transmission of Creutzfeldt–Jakob disease. GH was licensed for use in adults in March 1996.

GH therapy is contraindicated in cases of tumour activity and pregnancy. Side-effects may include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at the injection site.

Treatment with GH replacement is administered by a daily subcutaneous injection. The initial dose is between 0.6 and 0.9 IU (0.2–0.3 mg) and typically

0.8 IU (0.27 mg) daily. Dose adjustments are then determined by monthly assessments of GH-dependent hormone markers and the presence of adverse effects, for a period of 2–3 months until a maintenance dose is achieved. The median maintenance dose currently used is 1.2 IU (0.4 mg) daily.[1] Patients normally administer the injection themselves, and the site of the injection is normally the thigh. Requirements for GH replacement may decrease with age.

Chapter 2
Methods

Methods for reviewing effectiveness

The *a priori* methods used for the review are outlined in the research protocol (see appendix 1). This protocol was sent for expert comments to members of the advisory group for the review (see *Acknowledgements*). Helpful comments were received relating to the general content of the research protocol, but there were none that identified specific problems with the methods of the review.

Some points of clarification were made to the methods discussed in the original protocol.

- Criteria for considering studies for this review were that they were published randomised controlled trials (RCTs) of adults aged 18 years or over with GHD, in which the intervention was any dose of GH or placebo, with QoL outcome measures included.
- In addition to searching the databases, one of the key endocrinology journals, *Clinical Endocrinology*, was handsearched for both articles and conference abstracts in issues from 1993 to August 2000.
- References of all retrieved articles were searched, and relevant researchers were contacted to ensure that all eligible trials had been identified.

Sources of information, including databases searched and key search terms, can be found in appendix 2.

Studies identified by the search strategy were assessed for inclusion through three stages. Titles and abstracts were independently considered for inclusion by two reviewers. The full text of those studies included at this stage was examined for inclusion by two reviewers independently. Two reviewers extracted results independently. At each stage, any differences of opinion were resolved through discussion.

RCTs were assessed for quality using the Jadad scale[5] (see appendix 3). A list of excluded studies is given in appendix 4.

It is recognised that adults with GHD have decreased QoL. The term QoL has been used in this review in its widest sense to mean general health-related impact assessed from the patient's perspective and therefore may be regarded as health-related QoL. A range of instruments are used to measure health-related QoL, and they assess different dimensions of health status, including symptoms and functioning, psychiatric and mental health, and psychological aspects. An exception is the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA); this assessment tool adopts the needs-based model of QoL, which argues that QoL is the extent to which GHD prevents adults from fulfilling their needs. An overview of the various instruments used in the included studies is shown in appendix 5.

Most scales are generic (such as the Nottingham Health Profile [NHP] and the General Health Questionnaire [GHQ]) and are intended to apply to a wide range of health problems. It is difficult to interpret the meaningfulness of change scores of profiles such as these in the context of GHD. This difficulty has led to the development of objective disease-specific instruments, such as the QoL-AGHDA, but this assessment has not been widely used in trials to date.

Meta-analysis

Meta-analyses were performed to generate an estimate of the change in QoL with GH treatment, as opposed to placebo, in adults with GHD, based on a weighted average of the results from all the studies meeting the inclusion criteria and reporting data. Details of the methods used in the meta-analyses, including assumptions made when pooling data, are shown in appendix 1.

Methods for reviewing cost-effectiveness

Cost-effectiveness was assessed by a two-stage procedure. Firstly, economic evaluations were sought. No full economic evaluations were found or suitable data to model cost per quality-adjusted life-year (QALY) of GH treatment. A more limited model was constructed to

estimate the cost of GH replacement in adults in a UK setting using best available evidence. Full details of the search strategy and information sources for the economic analysis are outlined in appendix 2. Modelling details are discussed in chapter 4 of this report.

Chapter 3

Effectiveness

Quality and quantity of research on GH in adults

Seventeen published RCTs met the inclusion criteria for the review and are listed in *Table 1*.[6–22]

Twenty-three different QoL scales were utilised in the included studies to evaluate QoL. Only four of these QoL scales were used in three or more studies: the GHQ, Hamilton Depression Scale (HDS), NHP and its subscales, and Psychological General Well-Being (PGWB) Schedule. Seven studies provided numerical data that could be meta-analysed.

The RCTs are summarised in *Tables 2* and *3* and appendix 6. *Table 2* summarises those trials that reported data, and *Table 3* summarises the trials for which there were no data reported. If possible, reported doses have been converted to IU.

From *Tables 2* and *3*, it can be seen that there are a number of differences in trial designs for the included RCTs. A number of the included RCTs used a crossover design,[8,10,12,14,22] and wash-out periods ranged from no washout period to 3 months. The typical trial duration was 6 months,[6,8,9,11,13,15,16,19–21] with one trial duration less than this.[14] Only two of the included studies had trial durations of 1 year or more.[7,10] Sample sizes of trials were often small, with a range of sample sizes from 6[12] to 173[6], and the majority of trials had between 21 and 40 participants.

TABLE 1 *Trials included in the assessment of effectiveness of GH in adults*

Included studies	Number of patients	Outcomes (QoL scales)				
		GHQ	HDS	NHP	PGWB	Other
Attanasio *et al.*, 1997[6]	173			✔		
Baum *et al.*, 1998[7]	40	✔		✔	✔	MMPI-2
Bengtsson *et al.*, 1993[8]	10					CPRS, SCL-90 psychiatric interview
Beshyah *et al.*, 1995[9]	40	✔				CPRS
Burman *et al.*, 1995[10]	36			✔	✔	HSCL-56, spouse's questionnaire
Cuneo *et al.*, 1998[11]	163			✔		GHDQ
Degerblad *et al.*, 1990[12]	6					POMS, SMQ, psychiatric interview, finger tapping
Deijen *et al.*, 1996[13]	48					HSCL, POMS, STAI
Florkowski *et al.*, 1998[14]	20					DSQ, SCL-90, SAS
Giusti *et al.*, 1998[15]	26		✔			KSQ
McGauley, 1989[16]	24	✔		✔	✔	
McKenna *et al.*, 1997[17]	30			✔		AGHDA
McKenna *et al.*, 1997[18]	69			✔		AGHDA
de Novaes Soares *et al.*, 1999[19]	10		✔			SADS, BDI
Verhelst *et al.*, 1997[20]	148		✔			
Wallymahmed *et al.*, 1997[21]	35			✔		LFS, HADS, SES, MFS
Whitehead *et al.*, 1992[22]	14			✔	✔	

HDS, Hamilton Depression Scale; PGWB, Psychological General Well-Being (Schedule); MMPI, Minnesota Multiphasic Personality Inventory; CPRS, Comprehensive Psychological Rating Scale; SCL-90, Symptom Checklist 90; HSCL, Hopkins Symptom Checklist; GHDQ, Growth Hormone Deficiency Questionnaire; POMS, Profile of Mood States; SMQ, Sjoberg Mood Questionnaire; STAI, State–Trait Anxiety Inventory; DSQ, Disease-Specific Questionnaire; SAS, Social Adjustment Scale; KSQ, Kellner Symptom Questionnaire; SADS, Schedule for Affective Disorders and Schizophrenia; BDI, Beck Depression Inventory; LFS, Life Fulfilment Scale; HADS, Hospital Anxiety and Depression Scale; SES, Self-Esteem Scale; MFS, Mental Fatigue Scale

TABLE 2 *Summary of evidence of effectiveness of GH on QoL in adults (trials that reported data)*

Details of published RCTs	Instruments used	GH Score (mean ± SE)		Placebo Score (mean ± SE)	
		At start	At end	At start	At end
Baum *et al.*, 1998[7]	NHP:				
	Emotional reactions	7.8 ± 3.1	10.7 ± 4.9	12.0 ± 4.9	3.0 ± 1.7
Design: RCT, parallel	Energy	18.3 ± 6.2	15.6 ± 9.1	19.3 ± 8.2	8.9 ± 5.1
	Pain	3.1 ± 2.5	4.2 ± 2.9	12.5 ± 4.8	2.5 ± 1.8
Intervention: GH mean	Sleep	15.0 ± 5.6	8.0 ± 3.3	14.0 ± 5.1	10.7 ± 3.3
dose, 4 ± 2 μg/kg/day	Social isolation	3.2 ± 1.7	1.3 ± 1.3	3.0 ± 2.2	0.0 ± 0
(0.012 ± 0.006 IU/kg/day)	Physical mobility	5.3 ± 2.8	3.3 ± 1.9	10.5 ± 4.0	5.8 ± 3.0
Placebo					
n = 40	MMPI-2:				
For 18 months	Hypochondriasis	52 ± 10*	57 ± 9*	55 ± 11*	53 ± 11*
	Depression	55 ± 11*	54 ± 6*	55 ± 10*	55 ± 11*
Patients: AO-GHD,	Hysteria	52 ± 10*	57 ± 12*	55 ± 9*	53 ± 10*
multiple deficiencies,					
peak GH < 5 μg/l	PGWB	83 ± 13*	84 ± 18*	85 ± 16*	86 ± 8*
	GHQ	37 ± 17*	36 ± 19*	36 ± 19*	31 ± 8*
Jadad quality score: 5/5					
			At 18 months		At 18 months
Beshyah *et al.*, 1995[9]	Median GHQ (range)	3 (0–47)	1 (0–55)	12 (0–37)	4 (0–47)
	Median CPRS (range)	8 (4–34)	7 (1–23)	20 (3–31)	15 (3–23)
Design: RCT, parallel					
			At 6 months		At 6 months
Intervention:					
GH, 0.04 IU/kg/day					
Placebo					
n = 40					
For 6 months					
Patients: AO-GHD and					
CO-GHD, multiple deficiencies,					
GH peak < 6 mU/l					
Jadad quality score: 3/5					
Burman *et al.*, 1995[10]	NHP:				
	Mean NHP	16.7 ± 15.7*	10.4 ± 14.2*	16.7 ± 15.7*	14 ± 17.9*
Design: RCT, crossover	Emotions	23.1 ± 25.3*	12.1 ± 20.9*	23.1 ± 25.3*	16.5 ± 24.1*
	Sleep	13.4 ± 19.1*	12.7 ± 21.9*	13.4 ± 19.1*	15.3 ± 21.6*
Intervention:	Energy	37.1 ± 39.6*	16.4 ± 24.2*	37.1 ± 39.6*	25.1 ± 38.6*
GH mean dose, 2.4 U/day	Pain	8.7 ± 18.8*	8.7 ± 16.9*	8.7 ± 18.8*	8.8 ± 21.7*
Placebo	Social isolation	9.9 ± 21.9*	4.5 ± 14.6*	9.9 ± 21.9*	8.5 ± 19.6*
n = 36	Physical mobility	7.8 ± 11.2*	7.7 ± 12.6*	7.8 ± 11.2*	9.7 ± 14.4*
For 21 months					
	Mean HSCL	89	80.2	89	84
Patients: AO-GHD and	Mean PGWB	92 ± 15.5*	97.4 ± 15.4*	92 ± 15.5*	93.9 ± 16.6*
CO-GHD, multiple deficiencies,					
GH peak ≤ 3 μg/l			At 9 months		At 9 months
Jadad quality score: 2/5					

continued

***TABLE 2* contd** *Summary of evidence of effectiveness of GH on QoL in adults (trials that reported data)*

Details of published RCTs	Instruments used	GH Score (mean ± SE)		Placebo Score (mean ± SE)	
		At start	At end	At start	At end
Cuneo *et al*., 1998[11]	NHP:				
	Energy	1.03 ± 0.06	0.55 ± 0.05	1.17 ± 0.05	0.56 ± 0.04
Design: RCT, parallel	Pain	0.77 ± 0.1	0.34 ± 0.04	0.23 ± 0.06	0.28 ± 0.05
	Emotional reactions	1.38 ± 0.12	0.65 ± 0.07	0.70 ± 0.07	0.58 ± 0.05
Intervention:	Sleep	1.14 ± 0.07	0.85 ± 0.07	0.99 ± 0.06	0.55 ± 0.05
GH, 0.125 U/kg/week for first	Social isolation	0.48 ± 0.06	0.27 ± 0.04	0.24 ± 0.03	0.31 ± 0.04
week, then 0.25 U/kg/week	Physical mobility	0.54 ± 0.07	0.61 ± 0.06	0.38 ± 0.03	0.37 ± 0.05
Placebo					
n = 163			At 6 months		At 6 months
For 6 months					
Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak < 5 mU/l following Genotropin					
Jadad quality score: 4/5					
Degerblad *et al*., 1990[12]	SMQ:				
	Activity	2.78 ± 0.23	2.97 ± 0.28	2.70 ± 0.20	2.60 ± 0.18
Design: RCT, crossover	Social orientation	3.12 ± 0.13	2.92 ± 0.18	2.83 ± 0.12	2.95 ± 0.19
	Control	2.77 ± 0.19	2.97 ± 0.17	2.70 ± 0.16	2.72 ± 0.19
Intervention:	Extraversion	2.70 ± 0.12	2.82 ± 0.11	2.67 ± 0.08	2.57 ± 0.07
GH, 0.5–0.6 IU/kg/week	Calmness	2.53 ± 0.26	2.70 ± 0.14	2.60 ± 0.13	2.42 ± 0.17
(0.07–0.08 IU/kg/day)	Pleasantness	2.93 ± 0.16	2.76 ± 0.28	2.55 ± 0.12	2.58 ± 0.19
Placebo					
n = 6	POMS:				
For 12 weeks, then 12 weeks	Tension	2.67 ± 0.26	2.65 ± 0.25	2.60 ± 0.21	2.77 ± 0.29
of washout	Depression	2.17 ± 0.20	1.93 ± 0.24	2.47 ± 0.42	2.55 ± 0.39
	Anger	1.97 ± 0.23	2.10 ± 0.27	2.13 ± 0.39	2.50 ± 0.30
Patients: AO-GHD and	Fatigue	2.77 ± 0.24	2.50 ± 0.44	2.97 ± 0.34	2.93 ± 0.23
CO-GHD, GH peak ≤ 3.4 µg/l	Confusion	2.20 ± 0.28	2.40 ± 0.35	2.73 ± 0.31	2.58 ± 0.30
Jadad quality score: 3/5			At 6 months		At 6 months
Florkowski *et al*., 1998[14]	Mean SCL	5.8 ± 1.2	4.0 ± 0.7	3.7 ± 1.2	2.5 ± 0.8
	Mean SAS	2.05 ± 0.12	1.9 ± 0.13	1.86 ± 0.1	1.73 ± 0.08
Design: RCT, crossover	Mean DSQ	10.8 ± 2.43	8.1 ± 2.4	8.6 ± 1.7	5.0 ± 2.1
Intervention:			At 3 months		At 3 months
GH, ≤ 0.25 U/kg/week					
Placebo					
n = 20					
For 3 months					
Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak < 3 µg/l following clonidine					
Jadad quality score: 1/5					

continued

***TABLE 2* contd** *Summary of evidence of effectiveness of GH on QoL in adults (trials that reported data)*

Details of published RCTs	Instruments used	GH Score (mean ± SE)		Placebo Score (mean ± SE)	
		At start	At end	At start	At end
Giusti *et al.*, 1998[15]	Mean KSQ	23.8 ± 3.5	19.0 ± 4.0	24.4 ± 3.3	19.6 ± 3.5
	Mean HDS	27.9 ± 1.1	24.6 ± 0.8	28.6 ± 1.4	27.1 ± 1.1
Design: RCT, parallel					
	KSQ subscales:				
Intervention:	Anxiety	6.9 ± 1.2	5.6 ± 1.0	5.1 ± 0.8	4.5 ± 0.9
GH, 0.5–1 U/kg/?day	Depression	6.0 ± 1.3	4.0 ± 1.2	6.3 ± 1.0	4.5 ± 1.3
Placebo	Somatisation	6.6 ± 1.2	5.4 ± 1.3	9.9 ± 1.9	9.3 ± 2.3
n = 26	Hostility	4.9 ± 0.9	4.4 ± 1.2	2.3 ± 0.6	2.4 ± 0.6
For 6 months					
			At 6 months		At 6 months
Patients: AO-GHD, multiple deficiencies, GH peak < 3.5 µg/l					
Jadad quality score: 2/5					
de Novaes Soares *et al.*, 1999[19]	Mean HDS	7.6 ± 5.81*	2.2 ± 1.64*	4.75 ± 1.26*	2.5 ± 2.64*
	Mean BDI	12.6 ± 7.02*	4.2 ± 1.92*	7.0 ± 3.16*	4.5 ± 1.29*
Design: RCT, parallel					
			At 6 months		At 6 months
Intervention: GH, 0.125 then 0.25 IU/kg/week (0.018–0.036 IU/kg/day) Placebo *n* = 10 For 6 months					
Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak ≤ 4.5 ng/ml					
Jadad quality score: 3/5					
Wallymahmed *et al.*, 1997[21]	NHP:				
	Energy	1.76 ± 1.0	1.05 ± 0.9	1.30 ± 1.1	0.84 ± 1.2
Design: RCT, parallel	Emotional reactions	2.52 ± 2.9	1.82 ± 2.7	1.38 ± 1.5	1.53 ± 2.1
	Social isolation	0.52 ± 0.9	0.76 ± 1.2	0.62 ± 1.0	0.92 ± 1.4
Intervention:	Sleep	1.35 ± 1.4	1.41 ± 1.4	1.15 ± 1.3	1.00 ± 1.4
GH, 0.125 then 0.25 IU/kg/week	Pain	1.29 ± 2.1	2.0 ± 2.8	0.84 ± 1.3	1.15 ± 1.9
(0.018–0.036 IU/kg/day)	Physical mobility	0.88 ± 1.1	1.58 ± 1.8	0.61 ± 1.0	0.92 ± 1.2
Placebo					
n = 35	Impact Scale	22.1 ± 8.2	19.1 ± 7.5	22.1 ± 5.7	21.1 ± 7.3
For 6 months	LFS (personal)	34.0 ± 13.0	38.1 ± 16.6	29.6 ± 9.5	39.5 ± 13.4
	LFS (material)	11.1 ± 7.4	17.2 ± 14.6	9.6 ± 5.3	15.8 ± 12.7
Patients: AO-GHD and two	SES	27.8 ± 4.9	28.5 ± 5.9	28.4 ± 3.5	30.9 ± 4.4
patients with CO-GHD,	MFS	20.5 ± 8.9	18.2 ± 8.1	15.8 ± 4.3	15.5 ± 6.0
multiple deficiencies, GH peak	HAD (anxiety)	7.8 ± 3.4	7.3 ± 3.4	6.6 ± 2.9	5.5 ± 3.3
< 10 mU/l	HAD (depression)	5.5 ± 2.8	5.1 ± 3.2	4.6 ± 3.0	4.7 ± 4.5
Jadad quality score: 3/5			At 6 months		At 6 months

SE, standard error; SD, standard deviation

* *Results expressed as mean ± SD*

TABLE 3 *Summary of evidence of effectiveness of GH on QoL in adults (trials that did not report data)*

Details of published RCTs	Instruments used
Attanasio *et al.*, 1997[6] Design: RCT, parallel Intervention: GH mean dose ≤ 12.5 µg/kg/day (0.0375 IU/kg/day) Placebo *n* = 173 For 6 months Patients: AO-GHD and CO-GHD, multiple deficiencies, peak GH < 5 µg/l Jadad quality score: 2/5	NHP: Emotional reactions Energy Pain Sleep Social isolation Physical mobility
Bengtsson *et al.*, 1993[8] Design: RCT, crossover Intervention: GH, 0.25–0.5 U/kg/week Placebo *n* = 10 For 6 months Patients: AO-GHD, multiple deficiencies, ITT peak GH < 1 mU/l Jadad quality score: 4/5	CPRS SCL-90 Psychiatric interview
Deijen *et al.*, 1996[13] Design: RCT, parallel Intervention: GH, 1–3 IU/m^2 Placebo *n* = 48 males For 6 months Patients: all CO-GHD, some multiple deficiencies, GH peak < 7 µg/l Jadad quality score: 2/5	HSCL POMS STAI
McKenna *et al.*, 1997[17] Design: RCT, parallel Intervention: GH, 0.10–0.20 IU/kg/week (0.014–0.028 IU/kg/day) Placebo *n* = 30 For 6 months Patients: Not stated Jadad quality score: NA	NHP AGHDA

continued

***TABLE 3* contd** *Summary of evidence of effectiveness of GH on QoL in adults (trials that did not report data)*

Details of published RCTs	Instruments used
McKenna *et al.*, 1997[18] Design: RCT, parallel Intervention: GH, 0.125–0.250 IU/kg/week (0.018–0.036 IU/kg/day) Placebo *n* = 69 For 6 months Patients: Not stated Jadad quality score: NA	NHP AGHDA
McGauley, 1989[16] Design: RCT, parallel Intervention: GH, 0.07 IU/kg/?day Placebo *n* = 24 For 6 months Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak < 3 mU/l Jadad quality score: 2/5	Mean change in NHP PGWB GHQ
Verhelst *et al.*, 1997[20] Design: RCT, parallel Intervention: GH, 0.125–0.250 IU/kg/week (0.018–0.036 IU/kg/day) Placebo *n* = 148 For 6 months Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak < 10 mU/l Jadad quality score: 3/5	NHP
Whitehead *et al.*, 1997[22] Design: RCT, crossover Intervention: GH, 0.5 U/kg/week Placebo *n* = 14 For 6 months, 1-month washout, further 6 months Patients: AO-GHD and CO-GHD, multiple deficiencies, GH peak < 7 mU/l Jadad quality score: 2/5	NHP PGWB
NA, not applicable	

Three of the 17 studies had sample sizes of 10 or fewer.[8,12,19] In one parallel trial, the numbers of participants in the intervention and control groups were not stated,[7] and in a second, the numbers of participants in the groups were equal.[9]

Generally, the participants included in the trials were a mix of both CO- and AO-GHD. Only three trials included wholly AO-GHD,[7,8,15] and one trial had only CO-GHD participants.[13] The diagnosis of GHD in trials followed tests of tolerance to insulin, glucagon, clonidine or arginine, using a range of cut-off values from moderate to high. Two studies diagnosed GHD based on a GH level greater than the 9 mU/l for severe GHD recommended by the Society for Endocrinology.[21,20] However, three trials[12,13,19] did not give cut-off values for the diagnosis of GHD in their participants, rather giving the maximum GH level in response to the diagnostic test; and in two trials,[17,18] data for diagnostic cut-offs were not given. In all trials, participants with multiple and isolated deficiencies were included, except for two trials in which data were not given.[17,18]

A range of GH doses were used in the included RCTs; however, the reporting quality and differences in the unit of measurement expressed in some trials make overall description difficult. For example, some trials reported U/kg/time, others reported IU/kg/time, and others reported mg or µg/kg/time.[11,15,16,23] However, the typical GH dose in the majority of studies ranged from 0.25 to 0.5 IU/kg/week. In one study, the unit of measurement used was dose per square metre of body surface area,[13] and a range of doses were given because part of the objective of the trial was an evaluation of different doses. The reporting in one other study does not describe whether the dose of GH used was per kilogram body weight per week or per day, although it may be presumed from the dose that it was per day.[16] It is important to note that, in all the trials, the dose of GH replacement was defined by a unit of weight; this is no longer current practice because findings suggested that obese patients were often overdosed and many women were found to be underdosed.[24] Because all studies reported dose only in relation to a unit measure of weight, it is not possible to ascertain what proportion of patients were on a maintenance dose similar to that typically used in current practice (1.2 IU/day). In a number of trials, participants had previously received GH replacement therapy. All, however, had at least 12 months without treatment prior to the commencement of the trial.[6,11–14,19–21]

The QoL outcome measures used in the trials also varied but were typically self-report measures, although in some trials, clinical or semi-structured interviews took place.[9,15,19] In both these methods, there are the potential problems of bias inherent in any subjective measure, such as social desirability bias (which is the tendency to respond in a manner that is perceived to be the socially desirable response) and experimenter bias (which is the tendency to respond in a manner which is perceived to be how the experimenter requires). Test–retest reliability is reported to be high for most of these measures (see appendix 5), although it is important to note that small changes in scores may merely reflect differences over time rather than the treatment effect being measured.

Based upon the Jadad scale measuring the likelihood of trial bias, only one of the included trials was of very good quality (Jadad score, 5/5)[7], two trials were of good quality (4/5)[8,11] and only one trial was of poor quality (1/5).[14] In the latter study,[14] the trial was described as randomised, but the method of randomisation was not described, drop-outs and losses to follow-up were not stated, and although the patients were blinded, it was unclear whether the outcome assessors were blinded. The majority of included trials scored 3/5 or 2/5 for reasons such as describing the trial as randomised and/or double-blind but failing to elaborate upon the method of randomisation. The two remaining trials were published only as abstracts, and therefore it is impractical to measure the Jadad score.[17,18]

Assessment of clinical effectiveness measured by QoL

Nottingham Health Profile

Ten trials evaluated health-related QoL using the NHP. In six of these trials, no data were presented.[6,16–18,20,22] The remaining four trials all presented effect sizes for the individual six dimensions of the NHP.[7,10,11,21] In one data set,[10] the baseline NHP score was a combined score including both intervention and control groups, which makes interpretation difficult because there may have been differences between the two groups on this index at baseline. In the remaining three trials, there were often large differences in baseline measurements between intervention and placebo groups,[7,11,21] as can be seen in *Table 2*. For all the dimensions of the NHP, a decrease in score relates to better QoL.

Total NHP score

In one trial, Burman and co-workers[10] reported mean total NHP scores and showed a statistically

significant reduction (improvement) in mean total score in the intervention group (from 16.7 to 10.4, $p < 0.01$) and a non-significant reduction (improvement) in the control group at 9 months.

Energy

Four trials reported mean scores for the individual dimensions of the NHP (*Table 2*). On the energy dimension of the NHP, the Baum 1998 trial[7] demonstrated a reduction in energy score over the 18 months of the trial in both the intervention and control groups that was not, however, statistically significant. Reductions in energy scores were also demonstrated in the intervention groups of the Cuneo trial[11] (not statistically significant) and Wallymahmed trial.[21] In the latter trial, a statistically significant reduction was shown (mean score, from 1.76 to 1.05; $p < 0.01$). In both the Cuneo and Wallymahmed trials, non-significant reductions in energy score were also demonstrated in the control groups. In the Cuneo study, the reduction in energy score in the control group (from 1.17 to 0.56) was significantly greater than the reduction in the intervention group (from 1.03 to 0.55, $p < 0.05$). In the Burman study,[10] a significant reduction in energy score was demonstrated in both the intervention (from 37.1 to 16.4, $p < 0.003$) and placebo (from 37.1 to 25.1, $p < 0.04$) groups.

The four trials[7,10,11,21] that reported NHP energy subscale scores were pooled. There was marked heterogeneity. The summary estimate of changes in score was slightly in favour of placebo, but results were non-significant (see *Figure 1*). GH use was associated with a non-significant deterioration (score increase) of 0.29 points on the energy subscale (95% confidence interval [CI], –0.86 to 1.43).

Pain

On the pain dimension of the NHP, a rise in pain score was noted in the intervention group in the Baum study,[7] and a reduction was shown in the control group. These changes were not statistically significant and in part may reflect the vast differences in measurements taken at baseline. Increases in pain score in both the intervention and control groups were shown, but were not significant, in the Wallymahmed trial.[21] A reduction in pain score in the intervention group and a small increase in the control group were illustrated in the Cuneo trial[11] by a statistically significant treatment × time interaction effect ($p = 0.047$). No statistically significant increases or decreases in pain score were found in the Burman trial.[10]

The four trials[7,10,11,21] that reported NHP pain subscale scores were pooled. There was marked heterogeneity. The summary estimate of changes in score was in favour of placebo, but results were not statistically significant (see *Figure 2*). GH use was associated with a non-significant deterioration (score increase) of 3.04 points on the pain subscale (95% CI, –1.96 to 8.04).

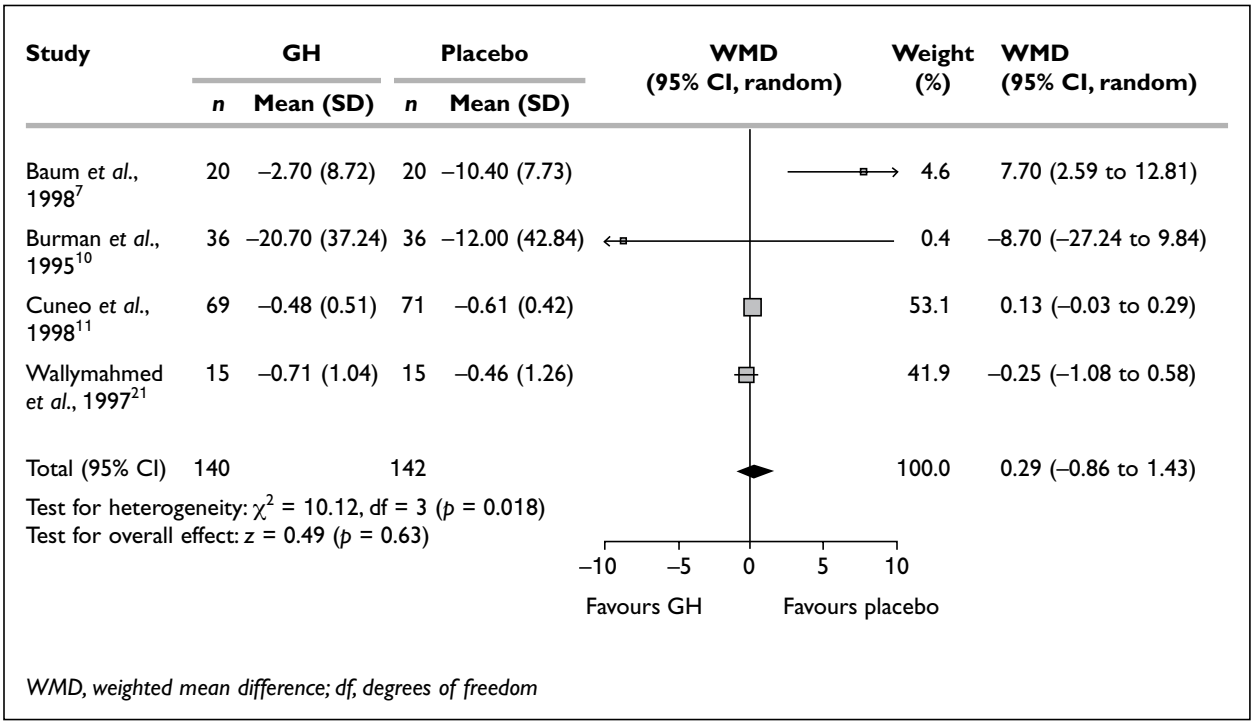

FIGURE 1 *Meta-analysis results for energy subscale of NHP*

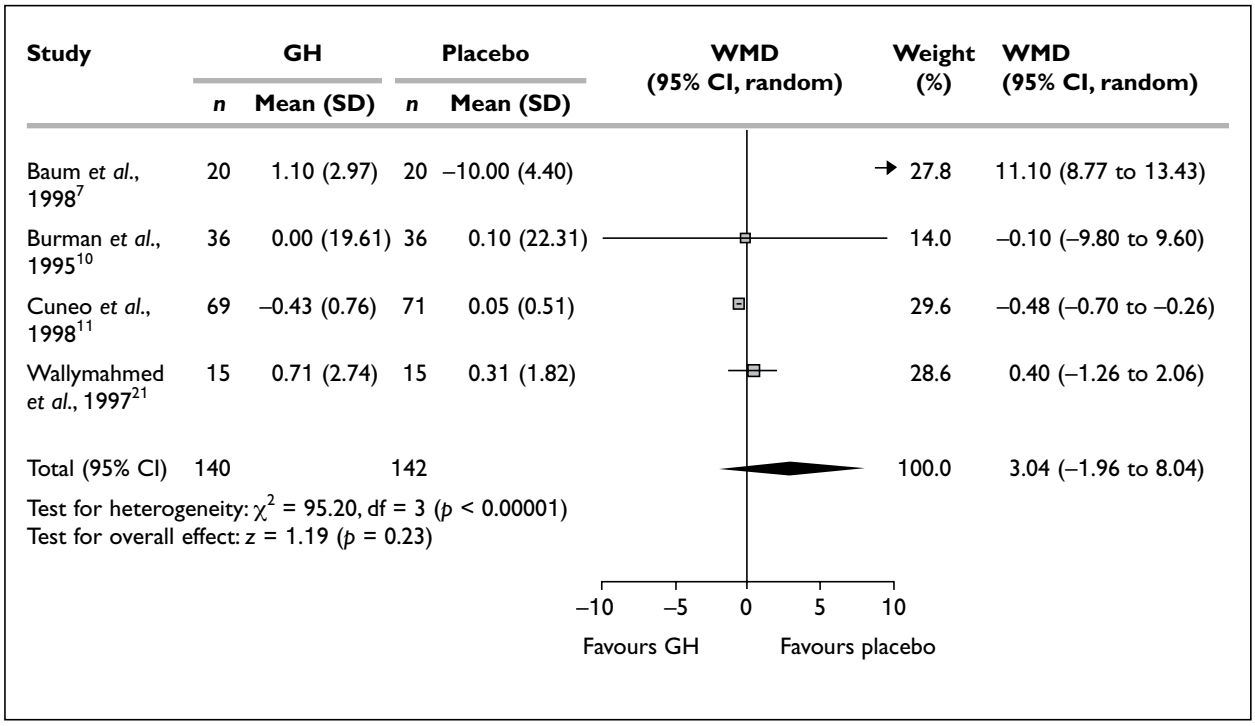

FIGURE 2 *Meta-analysis results for pain subscale of NHP*

Emotional reactions

Emotional reactions showed a reduction in score in the intervention groups of both the Cuneo[11] and Wallymahmed[21] trials. A reduction in score was also demonstrated in the control group of the Cuneo trial, but a small increase in score was shown in the control group of the Wallymahmed trial. An increase in emotional reaction score was also shown in the intervention group of the Baum study,[7] with a decrease in score in the control group. None of the changes in emotional reactions reached conventional statistical significance levels. Burman and co-workers[10] demonstrated a reduction in emotional reaction score in both the intervention and placebo groups that was statistically significant in the intervention group (from 23.1 to 12.1, $p < 0.003$).

The four trials[7,10,11,21] that reported NHP emotional reactions subscale scores were pooled. There was marked heterogeneity. The summary estimate of changes in score was in favour of placebo, but results were not statistically significant (see *Figure 3*). GH use was associated with a non-significant deterioration of 2.41 points on the emotional reaction subscale (95% CI, –2.78 to 7.61).

Sleep

A reduction in the sleep score of the NHP was shown in both the intervention and control groups in the Baum[7] and Cuneo[11] studies; this reduction was not statistically significant in either study. In contrast, in the Wallymahmed study,[21] the sleep score increased in the intervention group but fell in the control group. These changes in score were also not statistically significant. A small and non-significant reduction in sleep score was shown in the intervention group of the Burman study,[10] and a small increase was shown in the placebo group, which was also not significant.

The four trials[7,10,11,21] that reported NHP sleep subscale scores were pooled. There was some heterogeneity. The summary estimate of changes in score was very slightly in favour of placebo, but results were not statistically significant (see *Figure 4*). GH use was associated with a non-significant deterioration of 0.14 points on the sleep subscale (95% CI, –0.05 to 0.33).

Social isolation

The social isolation score showed non-significant increases in both the intervention and control groups of the Wallymahmed trial,[21] whereas the opposite effect occurred in the Baum study,[7] with a non-significant score decrease in both groups. In the Cuneo study,[11] a reduction in social isolation score was observed in the intervention group and an increase in the control group. Non-significant reductions in social isolation score were shown in both the placebo and GH groups of the Burman trial.[10]

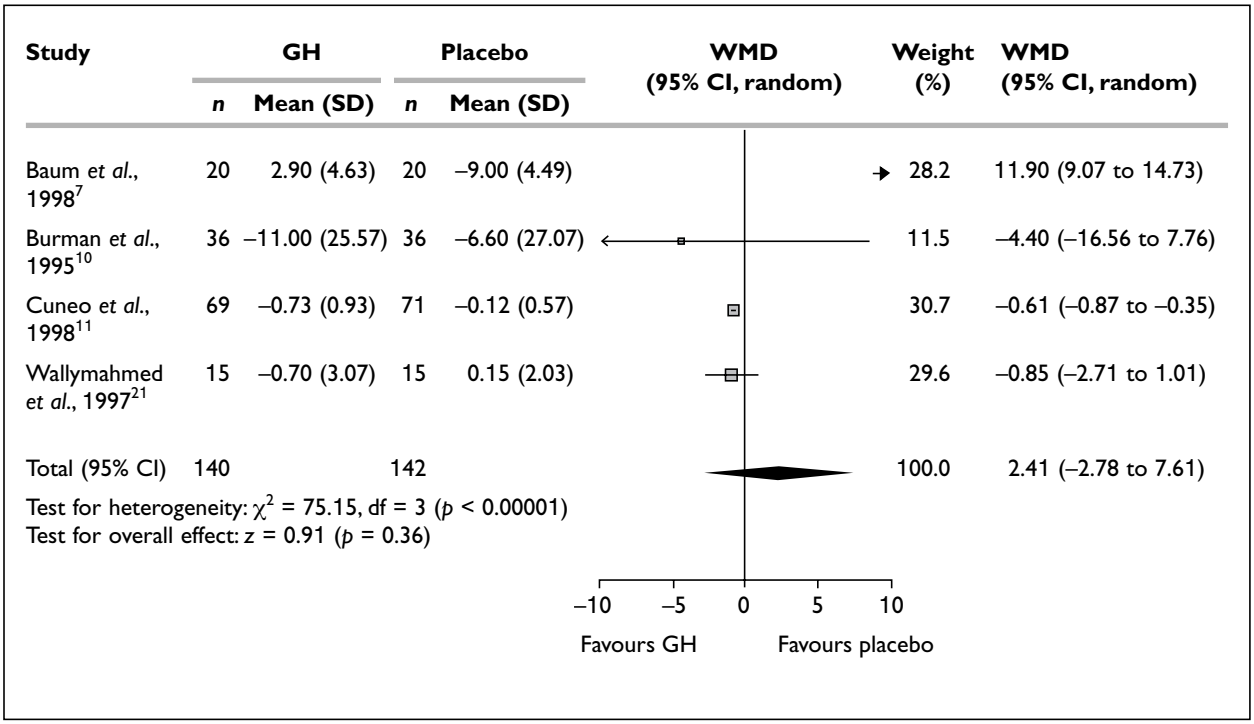

FIGURE 3 *Meta-analysis results for emotional reactions subscale of NHP*

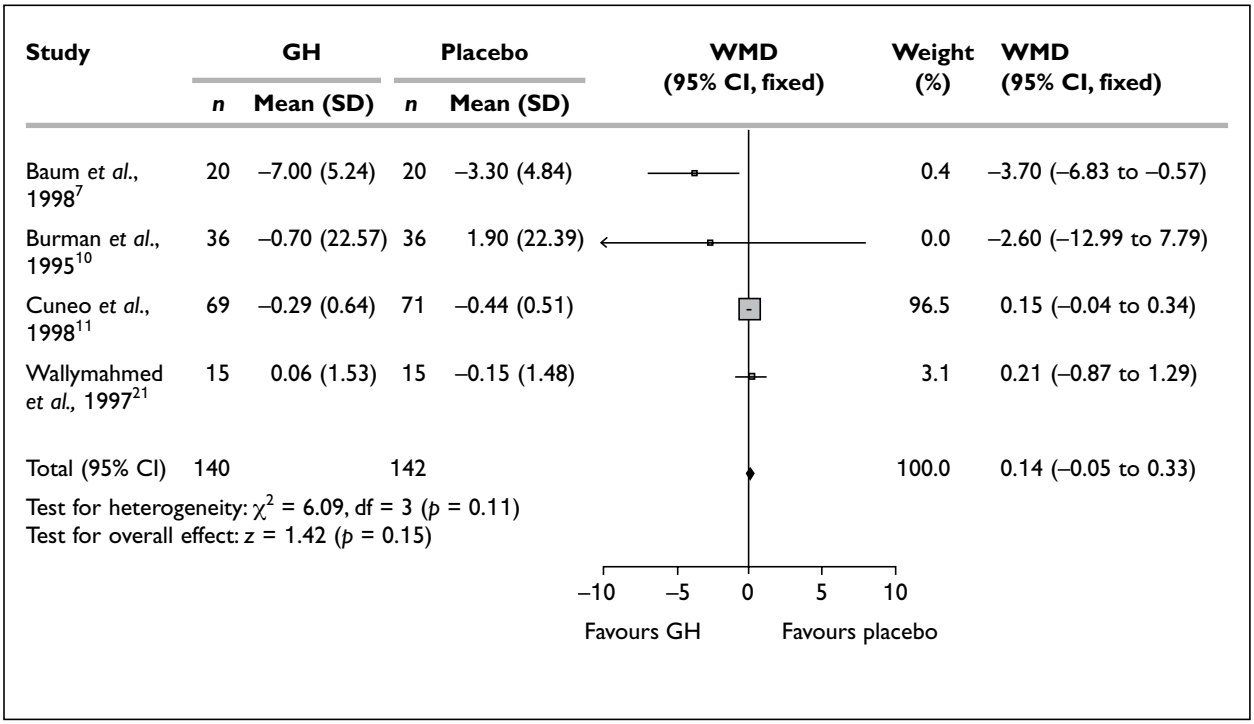

FIGURE 4 *Meta-analysis results for sleep subscale of NHP*

The four trials[7,10,11,21] that reported NHP social isolation subscale scores were pooled. There was some heterogeneity. The summary estimate of changes in score was in favour of GH treatment over placebo and was statistically significant (see *Figure 5*). GH use was associated with an improvement of 0.26 points on the social isolation subscale (95% CI, –0.39 to –0.12).

Physical mobility

Physical mobility scores showed non-significant increases in both the intervention and control groups of the Wallymahmed trial,[21] whereas again the opposite effect occurred in the Baum study,[7] with a non-significant score decrease in both groups. There was an increase in physical mobility scores in the intervention group and a small decrease in the control group in the Cuneo study.[11] No statistically significant differences in effects were shown. Physical activity score decreased in the intervention group and increased in the placebo group in the Burman study,[10] but differences were small and not statistically significant.

The four trials[7,10,11,21] that reported NHP physical mobility subscale scores were pooled. There was some heterogeneity. The summary estimate of changes in score was slightly in favour of placebo but was not statistically significant (see *Figure 6*). GH use was associated with a non-significant deterioration of 0.52 points on the physical mobility subscale (95% CI, –0.42 to 1.45).

General Health Questionnaire

Three included RCTs used the GHQ as an index of QoL.[7,9,16] In the GHQ, a reduction in score relates to increased QoL. In the McGauley study,[16] mean data were presented, but no separate baseline data were given for the intervention and control groups, making interpretation difficult. Therefore, these data are not described. The data from the Baum study[7] showed a small and non-significant reduction in mean GHQ score in both the control and intervention groups. In the Beshyah study,[9] a non-significant reduction in median GHQ score was shown in the intervention group, but a significant reduction was shown in the control group (from 12 to 4, $p < 0.05$).

The two trials[7,9] that reported GHQ scores were pooled. No heterogeneity was detected. The summary estimate of changes in score was in favour of placebo but was not statistically significant (see *Figure 7*). GH use was associated with a non-significant deterioration of 5.08 points on the GHQ (95% CI, –2.76 to 12.92).

Measures of depression

Depression in patients with GHD was an outcome measure used in five of the included RCTs. One trial used the BDI and the HDS,[19] and another used the HDS along with the depression dimension in the KSQ.[15] The remaining three trials measured depression as constituents in other psychological tests. Depression subscales of the

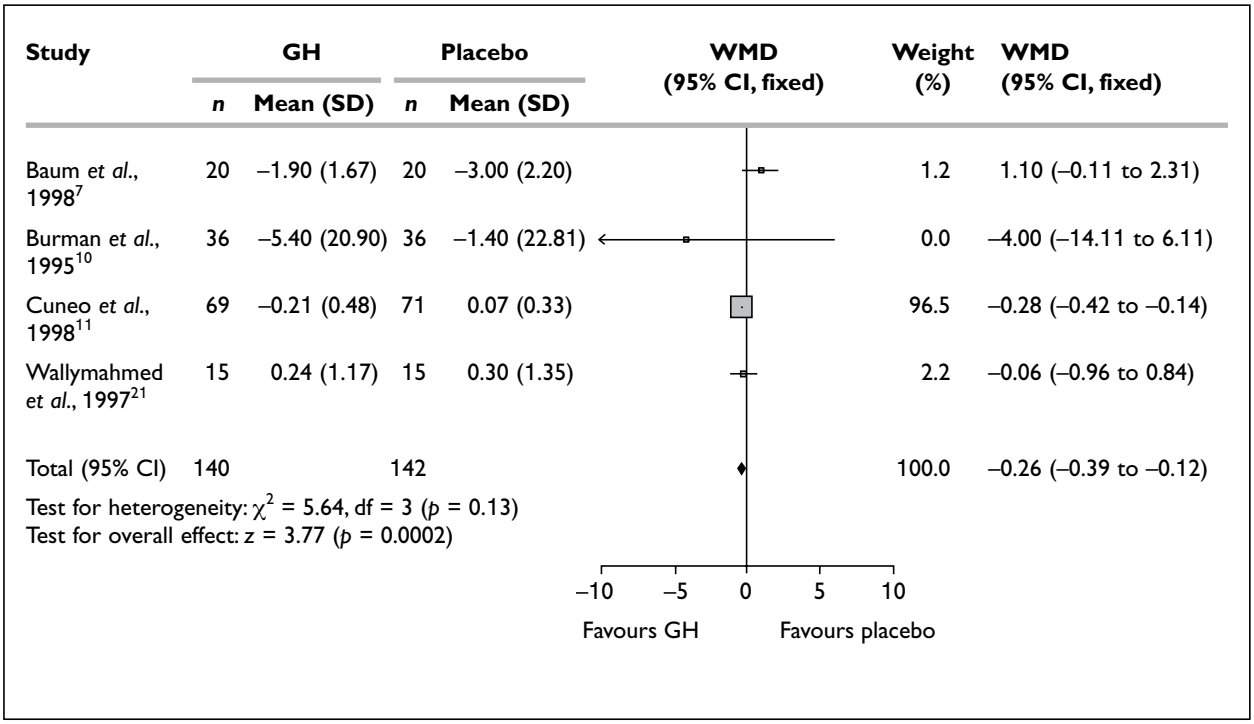

FIGURE 5 *Meta-analysis results for social isolation subscale of NHP*

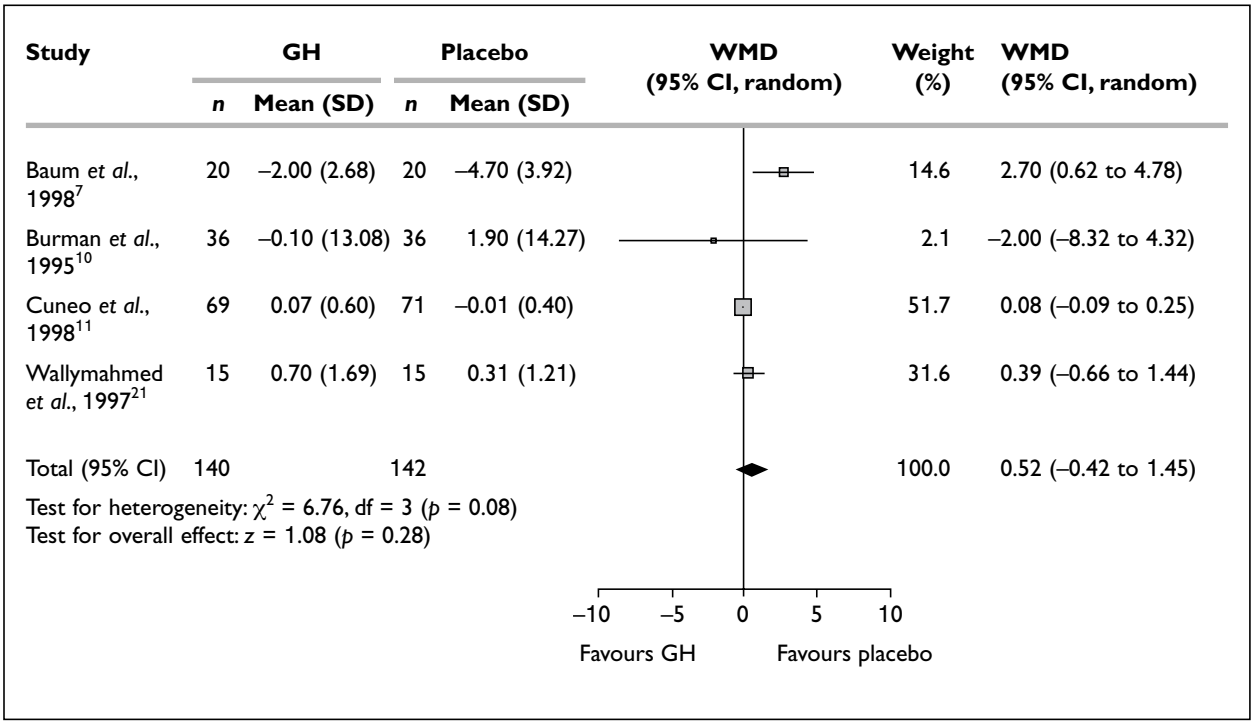

FIGURE 6 *Meta-analysis results for physical mobility subscale of NHP*

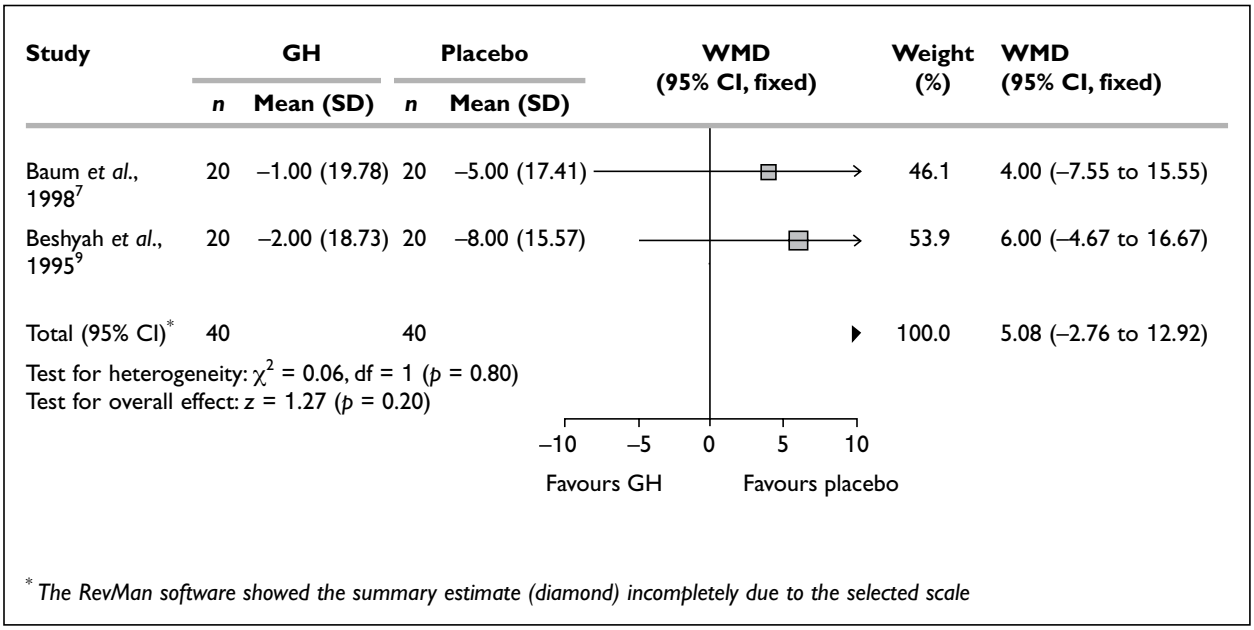

FIGURE 7 *Meta-analysis results for GHQ*

MMPI were used in one study,[7] POMS in one study[12] and the MFS in one other.[21] These items all use different scales of measurement, and thus it is difficult to gain an overall picture of the effects of GH replacement therapy on scores of depression. As such, the results of the studies will be described as general increases or decreases in score. It is also important to consider the known validity and reliability of the different scales. The BDI, MMPI and POMS are all demonstrated to have good reliability and validity; the KSQ has not seen as much validation, but results are deemed to be good; and little work has been undertaken on the MFS (see appendix 5).

No statistically significant effects on depression were shown by Baum and co-workers[7] (as measured by the depression dimension of the MMPI), by Wallymahmed and colleagues[21] (as measured by the MFS) or by Giusti and co-workers[15] (as

measured by the KSQ). Degerblad and colleagues[12] (using the depression dimension of POMS) demonstrated reduced scores in the intervention groups and an increase in the placebo groups, but this reduction did not reach statistical significance.

Using the HDS, Giusti and co-workers[15] found a significant reduction in depression in the GH-treated group, which signifies improvement in QoL (from 27.9 to 24.6, $p < 0.02$). There were no statistically significant differences in baseline measurements between the intervention and control groups. Similar results were found by de Novaes Soares and colleagues[19] using the HDS, with a reduction observed in both groups, but this reduction was statistically significant only in the intervention group (from 7.6 to 2.20, $p < 0.043$). Again, there were no statistically significant differences in baseline measurements between the two groups. In the de Novaes Soares study, a similar pattern of results was found using the BDI. There was a reduction in score in both the intervention and control groups, which was significant in the intervention group (from 12.6 to 4.2, $p < 0.043$), with no statistically significant differences at baseline. It is interesting that, although there were no significant differences at baseline in the de Novaes Soares study, baseline scores in the intervention group were greater than in the control group (HDS scores of 7.6 vs 4.75 and BDI scores of 12.6 vs 7.0, respectively), which may account for the statistically significant finding when compared to the score at 6 months. At 6 months, both intervention and control group scores were reduced to approximately the same values.

The two trials[15,19] that reported HDS were pooled. No heterogeneity was detected. The summary estimate of changes in score was in favour of GH but was non-significant (see *Figure 8*). GH use was associated with a non-significant improvement of 2.43 points on the HDS (95% CI, –4.94 to 0.07).

Other QoL indices

Four studies used the PGWB Schedule. Burman and co-workers[10] found a significant increase in well-being (indicated by an increase in score from 92.0 to 97.4, $p < 0.05$) in the intervention group but a non-significant increase in well-being in the placebo group. Baum and co-workers[7] showed no significant increases in well-being in either the intervention or placebo groups, and Whitehead and colleagues[22] did not present any data. In the McGauley study,[16] no separate baseline measurements for the two groups were presented.

The two studies[7,10] reporting PGWB were pooled. No heterogeneity was detected. The summary estimate of changes in score was in favour of GH, although results were not statistically significant (see *Figure 9*). GH use was associated with a non-significant improvement of 2.14 points on the PGWB (95% CI, –4.10 to 8.38).

The HSCL/SCL was used in only two of the included RCTs.[10,14] One study[10] found a significant reduction (improvement) in the HSCL-56 total score in the GH-treated group (from 89 to 80.2, $p < 0.001$). In the other study,[14] using the SCL, no significant reduction in symptoms was demonstrated. Similarly, in the one study that used the CPRS, no significant change in total score was found.

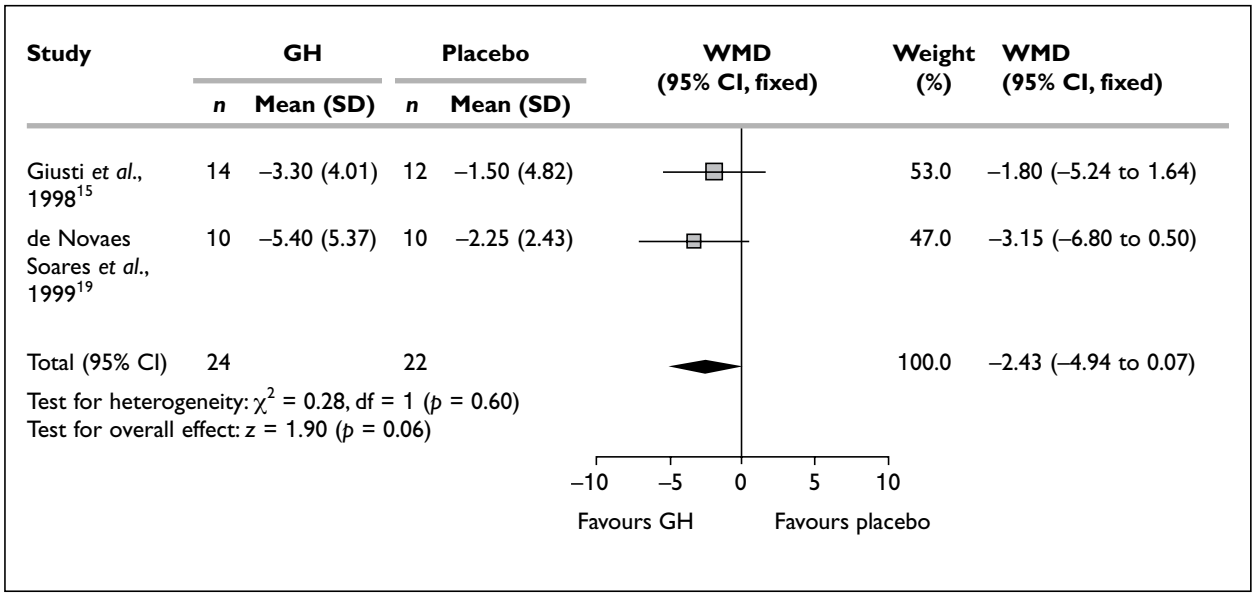

FIGURE 8 *Meta-analysis results for HDS*

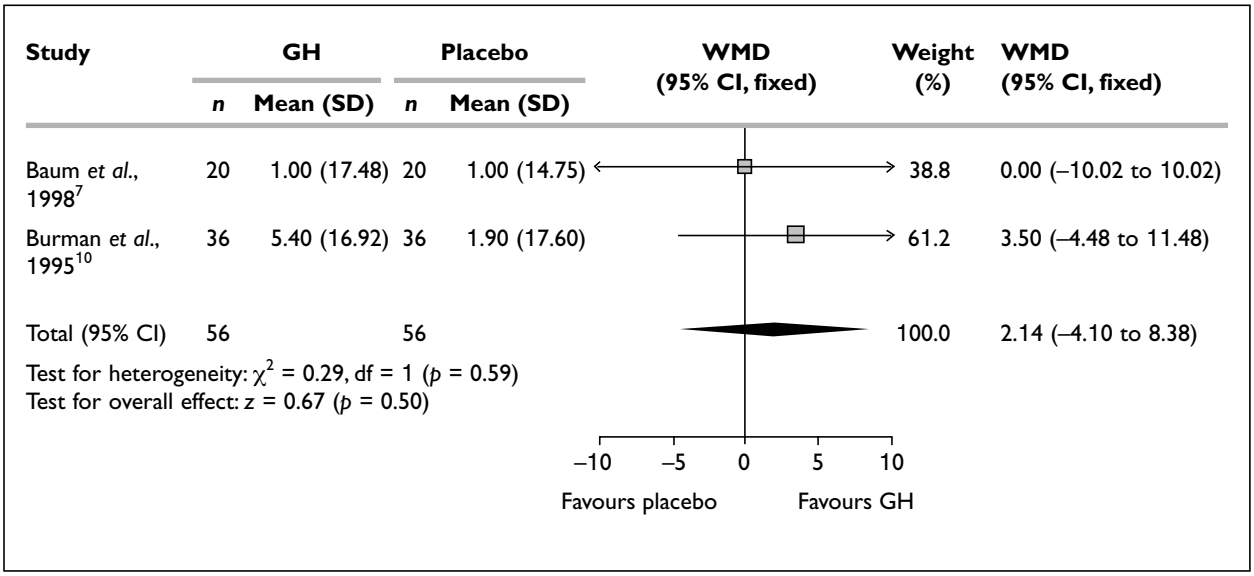

FIGURE 9 *Meta-analysis results for PGWB Schedule*

The results of these studies were not subject to meta-analysis. In the two McKenna trials,[17,18] the AGHDA scale was used, but results were not reported for the randomised controlled part of the study; only those results for a combined placebo and intervention group at the end of an open trial were given.

Adverse effects and safety

Adverse effects in the included trials

Adverse events are especially important in QoL trials of GH because:

- there are some fairly GH-specific adverse effects that occur in the short term and that are obvious to patients (e.g. fluid retention/ oedema and arthralgia)
- these adverse effects have the potential to unblind patients, even if trials are placebo controlled and patients are not told which treatment they are receiving
- such unblinding could produce biased assessments of treatment effects, particularly when the outcomes are self-assessed.

Various event rates for selected adverse events were reported in the included trials of GH in adults. Adverse effects for individual trials can be found in appendix 6. However, the quality of reporting adverse events was variable and not consistent across trials, with few descriptions of how clinical adverse events were defined, and in all but one crossover trial, adverse event data were not separated between GH and placebo groups.[8,10,12,14] Due to these issues and the different trial designs (e.g. dose ranges and administration), it is not possible to rank the studies in terms of the effect of adverse events on unblinding and therefore the risk of bias and overestimation of treatment effect. However, descriptions of the rates of adverse events for oedema and arthralgia are given here, and summary tables for these rates can be found in appendix 7. In general, the presence of adverse events in a patient with GHD would lead to a reduction in GH dose.[2,24]

Oedema

Rates of oedema in the trials that reported data were consistently higher in the participants receiving GH replacement than in those in the placebo groups. In the Baum study,[7] no reports of oedema were noted in the placebo group, while 10% of patients in the intervention group reported oedema. In the Attanasio trial,[6] rates of oedema were described separately for patients with AO-GHD and patients with CO-GHD. The rate of oedema in the patients with AO-GHD was shown to be greater in the GH replacement group than in the placebo group (an increase of 24.5%); in those with CO-GHD, the rate of oedema was 6.3% in the GH replacement group and nil in the placebo group. In the Beshyah trial,[9] there were 15% more reports of oedema in the GH replacement group compared with the placebo group; in the Cuneo trial,[11] this rate increase was 18%; and in the Verhelst trial,[20] the increase was nearly 17%.

Arthralgia

Rates of arthralgia in the trials that reported data were also found to be higher in the participants receiving GH replacement than in the placebo

groups, except in the Baum trial,[7] which reported no events of arthralgia. In the Attanasio trial,[6] the reported rates of arthralgia in the participants with AO-GHD were 16.6% higher in those receiving GH replacement compared with those in the placebo group; in the participants with CO-GHD, 6.3% of those receiving GH replacement reported arthralgia compared with none in the placebo group. Beshyah and co-workers[9] reported rates of arthralgia as nil in the placebo group and 10% in the GH replacement group, and Verhelst and colleagues[20] and Cuneo and co-workers[11] also reported increased rates of arthralgia in the GH groups compared to the placebo groups (increases of 13% and 17%, respectively).

Other safety issues

More research is needed on the long-term safety of GH replacement in relation to cancer, glucose regulation and high-dose pharmacological treatment. Based on currently available evidence, short-term GH replacement therapy using low, set doses does not appear to pose serious threats to the safety of treated patients.

A more complete discussion of safety issues relating to GH replacement therapy can be found in appendix 8.

Summary of the use of GH in adults with GHD

- In total, 17 RCTs considering the effect of GH on QoL in adults are included in the review (total of 892 patients). The RCTs were of variable quality, and most studies included both AO- and CO-GHD. Twenty-three QoL scales were used. Not all studies reported data.
- The trials using the NHP varied in terms of the quality of the study, trial duration and number of participants. Jadad quality scores were 5/5 and 4/5 in the Baum[7] and Cuneo[11] studies, respectively, while two trials (the Wallymahmed[21] and Verhelst[20] trials) scored 3/5, and the rest scored 2/5. Trial duration ranged from 6 to 21 months, and the number of participants ranged from 35 in the Wallymahmed trial[21] to 163 in the Cuneo trial.[11]
- One trial, Burman and co-workers,[10] reported mean NHP total scores and showed a statistically significant reduction (i.e. improved QoL) in the GH-treated group (from 16.7 to 10.4, $p < 0.01$) and a non-significant reduction in the control group at 9 months.
- The analysis of the individual dimensions of the NHP demonstrated statistically significant improvements in the GH replacement group compared with the control group for pain (Cuneo trial[11]), emotional reactions (Cuneo trial[11]) and sleep (Baum trial[7]). Conversely, there were improvements in the control group relative to the GH replacement group for energy, pain, emotional reactions and physical mobility (Baum trial[7]).
- Meta-analysis of four trials reporting NHP results found differences in favour of GH, with statistically significant results only in the social isolation dimension of the NHP: an improvement of 0.26 points (95% CI, –0.39 to –0.12).
- Meta-analysis of two trials reporting HDS results found differences in favour of GH treatment, but results were not statistically significant. GH use was associated with a non-significant improvement of 2.43 points (95% CI, –4.94 to 0.07).
- Meta-analysis of two trials reporting psychological well-being found differences in favour of GH, but results were not statistically significant. GH use was associated with a non-significant improvement of 2.14 points (95% CI, –4.10 to 8.38).
- There were a large number of other non-significant results.
- Adverse event data show that there is a 10–25% increase in reports of oedema and a 10–17% increase in reports of arthralgia in GH-treated groups compared with control groups.

Chapter 4
Economic analysis

Approach

The cost-effectiveness of GH replacement treatment for GH-deficient adults, either continuing treatment from childhood (CO-GHD) or with GHD of adult onset (AO-GHD), was considered. The first stage was to identify, synthesise and critique existing published economic evaluation evidence. Then, depending on these findings, it was necessary to decide how best to derive an estimate of cost-effectiveness from the point of view of the NHS and Personal Social Services sectors in England and Wales. It was anticipated that this would require either (1) adapting existing cost-effectiveness models, if they existed, or (2) if these models did not exist or were inappropriate, building a cost-effectiveness model for each condition by synthesising the best available economic and effectiveness evidence along with current epidemiological data and patterns of service use applicable to England and Wales.

Sources of information needed to inform economic modelling are broader than for an initial review of the economic evaluation evidence. Thus, it was a requirement to supplement the primary literature search and review with additional studies on resource use, costs and benefits that, although not economic evaluations, were considered useful for populating models.

When building or assessing a cost-effectiveness/cost–utility model, the modeller requires an outcome measure that adheres to certain properties. One property is an instrument that measures the outcome of an intervention as close as possible to the 'final' impact on health and that can measure this outcome in meaningful units. A second property is that the measure must be sensitive to important treatment and group differences. A third property is that, if the relevant health outcome is a multi-dimensional quality- and quantity-of-life construct, then the QoL measure must have interval properties that generate a summary index (of known reliability and validity) to measure the overall impact.

The primary objective of GH replacement treatment for adults with GHD is to improve QoL. Careful attention must be paid to the properties of the QoL measures currently in use before deciding whether the cost-effectiveness/cost–utility of GH replacement treatment can be adequately reviewed or modelled.

RCT evidence of the effectiveness of GH replacement treatment has used five main QoL measures: the GHQ, NHP, HDS, PGWB and AGHDA (see chapter 3). All these measures are problematical for economic evaluation. Interviews of GH-deficient adults revealed their most frequently perceived problems to be lack of energy, problems with memory and attention, irritability, poor self-confidence and self-esteem, reluctance to participate in social activities, and low motivation and sexual drive.[25] The GHQ is designed to detect psychiatric illness and has a limited focus on other QoL dimensions. Thus, this questionnaire was not considered sensitive enough to measure all relevant aspects of affected QoL in GH-deficient adults or QoL changes brought about from active treatment. The NHP is a generic measure with six dimensions of QoL (physical mobility, pain, social isolation, emotional reactions, energy and sleep). However, the scores for each dimension are separate and do not have interval properties. These factors make interpretation of scores difficult. The ordinal nature of the instrument (i.e. a simple yes/no answer to questions) means it is potentially insensitive to small improvements in QoL (see appendix 5). The HDS is designed to assess the severity of depression and is potentially unresponsive to the problems of GH-deficient adults. The PGWB is a generic multi-attribute QoL instrument with six subscales (anxiety, depressed mood, positive well-being, self-control, general health and vitality). The main disadvantage of the scale is that it does not cover social and physical well-being.[26] For these reasons, the measure was also considered inappropriate for the economic assessment of GH treatment. Other QoL instruments identified in the review of RCTs had mainly focused on single or limited aspects of well-being (e.g. anxiety, depression, social isolation or energy) but were not regarded as comprehensive measures for assessing GH replacement.

A potentially more sensitive instrument, the QoL-AGHDA, was investigated for possible use

in cost-effectiveness/cost–utility analysis. The QoL-AGHDA is a disease-specific instrument with potential to be a QoL index with interval measurement properties[27] and thus an appropriate effectiveness measure for cost-effectiveness analysis. The QoL-AGHDA was developed by interviewing GH-deficient patients and comprises 25 dichotomous questions about aspects of QoL directly relevant to GHD (i.e. lack of assertiveness, concentration, memory and energy; increased anxiety and depression, and difficulties in social interactions). An individual may score from 0 to 25, and the higher the score the worse the QoL. Research to date demonstrates: good reliability (high test–retest correlation), good validity (discriminates between treated and untreated patients with GHD; good correlation with other instruments such as PGWB and NHP dimensions of energy level, emotional reactions and physical mobility); and justification for the uni-dimensionality of the scale (high item–total correlations).[25] For these reasons, a focused systematic review of QoL studies that used the QoL-AGHDA instrument was undertaken to include studies other than RCTs.

Literature review

A broad search strategy was used to identify economic evaluations, costs, QoL and separate utility studies (see appendix 2). The literature reviews were carried out from an NHS and Personal Social Services perspective regarding costs, and from the societal (GH-deficient adults/society) perspective regarding benefits. The search yielded one supposed cost–utility study[28] and a limited number of other studies to inform modelling. The cost–utility study was the outdated Wessex Development and Evaluation Committee (DEC) Report No. 47,[28] which had been subsequently replaced by Wessex DEC Report No. 75.[29] This study did not present an economic evaluation. The 'utility' element of the earlier evaluation[28] was a set of scenarios not based on primary or secondary data sources, and thus could not be considered reliable or valid. There were three published cost studies,[29–31] four cost of pituitary illness studies[32–35] and 12 studies that investigated the QoL of GH-deficient adults (including patients with hypopituitary illness) using the QoL-AGHDA instrument. Four of the 12 studies investigated the impact of GHD on QoL by comparing QoL in GH-deficient adults and general adult populations[27,36–38] or patients with active acromegaly,[38] and eight studies (one reported in two publications) assessed the reliability and construct validity of the QoL-AGHDA[25] or the impact of GH replacement treatment on the QoL of GH-deficient adults.[17,18,25,39–44]

Cost studies

The three cost studies identified were UK based: one reported the cost of diagnosis, GH replacement treatment and monitoring,[29] and the others reported drug costs.[30,31] All these studies reported the cost of the drug as the main factor determining treatment cost (around 90% of the total cost[29]). One study reported that annual treatment costs per patient (1997 prices) could vary between £3472 and £6943 (GH dose, 0.125–0.25 IU/kg/week) and that costs were sensitive to assumptions about continuation rate and the price of somatropin.[29] For example, one study[45] showed that if only 46% of patients who were initially administered GH replacement treatment then continued therapy after 6 months, the annual cost of initial treatment would be lower, somewhere between £2600 and £5500. If the pharmaceutical company bore the drug cost for the first 3 months of a patient's treatment, first-year treatment would cost the NHS less (£2700–5600 per patient, and £2000–4200 per patient per annum thereafter).[29] The studies reporting annual drug costs of GH replacement[30,31] used more up-to-date drug doses and reported costs for a median dose of GH in the range of £3300–3453. Even so, study results are now a few years out of date. It is important to revise cost estimates in light of changes to clinical practice (particularly with regard to drug doses) and drug prices, as well as knowledge about continuation of treatment. Further investigation of uncertainty in reported cost estimates would also be helpful with regard to the duration of treatment and discounting.

The four studies considering the cost of hypopituitary illness analysed healthcare costs (i.e. primary and secondary care) and non-healthcare costs (i.e. loss of productivity) by comparing general populations versus adults with hypopituitary illness. The studies showed patients with hypopituitary illness had increased healthcare costs and increased numbers of sick days,[32–35] higher rates of unemployment[32] and more disability payments[32,34] per year. Unfortunately, each study design was flawed because the true additional costs of GHD could not be assessed.

QoL studies using QoL-AGHDA

Evidence of discriminant validity was shown by higher QoL-AGHDA scores reported for GH-

deficient patients than general population samples. Study patients were predominantly adult-onset patients with severe GHD and were treated for pituitary hormone deficiencies in addition to GHD (see appendix 9). In addition to a general public group, the study by Barkan[38] used a third group of patients (i.e. patients with acromegaly, who have excess GH) and showed that QoL-AGHDA scores were similar in GHD and acromegaly.

The impact of GH treatment on QoL was more difficult to interpret. Patients in these studies were prospectively followed, and a statistically significant positive GH treatment effect was demonstrated. Unfortunately, however, study designs could have biased results (see appendix 9). Six of the eight studies used designs that were not robust (i.e. were not randomised, placebo-controlled or even controlled), thus preventing the exclusion of confounding by possible placebo effect or other co-factors.[38] The other two studies (available as poster abstracts only) used randomised study design, but they did not report the results for the placebo and GH treatment groups. Instead, they reported the results for all patients at the start of the study and at the end of the study, when all the patients had been treated with GH for at least 6 months.[17,18]

More recent research has raised two important concerns about the use of QoL scores and the QoL-AGHDA instrument in particular.[27] The first is that researchers investigating the properties of the QoL-AGHDA raw data have suggested that its validity is restricted to use in analyses in which the sample is the same at all timepoints. To compare the QoL of different patient groups and at different timepoints, raw data should be transformed using the Rasch transformation method. This transformation generates a scale with additive properties and the ability to interpret mean and standard deviation values meaningfully in these comparative contexts. However, detailed research is currently lacking with respect to the interpretation of raw scores generated by other QoL measures, but this certainly needs to be examined. As such, while this study and other studies demonstrate a positive treatment effect of GH treatment on QoL, it could be misleading to use raw data for the purposes of economic evaluation, especially if comparison is to be made across patient groups or even wider.

The second concern is that the construct validity of the QoL-AGHDA instrument has been questioned.[27] It is probable that some items duplicate some aspects of QoL. Overall, it would seem the QoL-AGHDA instrument has better psychometric properties than other outcome measures and is easy to use, and therefore it has potential for use as an effectiveness measure; however, its use for economic evaluation assessment currently is somewhat premature.

Overall, the review of economic and related QoL studies led the review team to conclude that, while a cost–utility analysis would be a desirable basis on which to evaluate GH treatment in adults suffering from AO- or CO-GHD, it would not be possible, with the current evidence available, to generate cost per QALY data from a plausible cost–utility model. The limitations discussed above have outlined the reasons for this conclusion.

Modelling

A more limited model was built to provide information about the costs associated with GH treatment for GH-deficient adults either continuing treatment from childhood or with AO-GHD. This model will be an important component for future modelling of cost–utility analysis and for providing a platform to assess the budgetary impact analysis.

The purpose of the cost model was to analyse average total lifetime and annual costs of GH replacement for a patient starting treatment. The cost model presented was developed from the NHS and Personal Social Services perspective and updates existing analysis,[29] but provides greater flexibility by testing the sensitivity of the estimates more exhaustively and by analysing additional scenarios. The model is based on usual clinical practice for diagnosis, GH replacement treatment and monitoring in England and Wales, and uses simple decision analysis to structure the model. The best evidence or assumptions available at the time of the review have been used to populate the model. Any assumptions made by the modellers are explicit and kept to a minimum. The model was constructed in Excel™ 2000 software and is available in electronic format. Factors affecting uptake of treatment (i.e. the proportion of the GH-deficient population offered and accepting treatment) are only relevant for budgetary impact analysis.

An alternative of 'no treatment' was compared with treatment, and it was assumed there were no costs associated with the 'no treatment' alternative, at least to the NHS and Personal Social Services. This assumption is consistent with the fact

that, in practice, most of the GH-deficient patients with hypopituitary illness are treated and monitored regularly for their other health conditions.

The cost model incorporates the direct cost of diagnosis, GH therapy and monitoring associated with the treatment of GHD, but the evidence was not sufficiently robust to include possible differences in the use of other healthcare services due to GH treatment (e.g. hospitalisations). In addition, some experts have advised that, in practice, most patients with AO-GHD can be diagnosed and monitored concurrently with other medical problems, and thus not all healthcare contacts or procedures (e.g. endocrinology outpatient visits, blood tests and magnetic resonance imaging [MRI] scans) are specific to GHD diagnosis and monitoring. This makes it difficult to attribute true GHD diagnosis and monitoring costs. A scenario was used to explore the impact of overestimating true diagnosis and monitoring costs. Any possible savings from hospitalisations are considered as part of the budgetary impact analysis.

Patients with CO-GHD and those with AO-GHD require similar types of resources for treatment (i.e. the same GH dose and monitoring). The main difference between these patients relates to the length of treatment. Usually treatment is longer for patients with CO-GHD because the condition is present when the individual enters adulthood, whereas the AO-GHD condition results from hypopituitary abnormalities that, on average, develop later in life. As discussed above, there may also be differences in diagnosis because AO-GHD is usually linked with other hypopituitary conditions.

Although there is evidence that GH replacement has adverse side-effects (e.g. arthralgia, oedema, mild hypertension and carpal tunnel syndrome),[31] there is no additional treatment required for these conditions except GH dose adjustment. The model uses average GH doses, which are reported as representative for the current practice in the UK and tend to be titrated to minimise side-effects.

The average cost of diagnosis and annual cost of treatment (for first year and subsequent years) are reported for a GH-deficient patient. The total expected costs of treatment for patients with CO-GHD versus AO-GHD are reported assuming treatment duration (from average age at the start of GH replacement until death; see *Table 4*) of 59.5 years versus 37.5 years, respectively. Although there is some evidence to suggest that patients with hypopituitary illness have higher mortality, this analysis assumed that the average sex-adjusted life expectancy for the population of England and Wales applied to treated patients (and by implication untreated patients).

Treatment pathway

Figure 10 describes the expected treatment pathway that was used to structure the model. Sources for the pathway are: the position statement from the Society for Endocrinology on "The use of growth hormone replacement in adult patients with severe growth hormone deficiency",[3] a briefing paper on adult GH replacement from the same organisation[1] and local advice from an NHS consultant in endocrinology (Southampton General Hospital, Southampton: personal communication, 2001). These sources were used to identify and quantify the resource items (i.e. different types and quantities of healthcare contacts, tests, drug regimen, etc.).

If GHD is suspected, patients undergo some form of GH stimulation testing (insulin, or glucagon if insulin is contraindicated), possibly an MRI scan, BMD test and blood testing (IGF-I, glucose, HbA_{1C}, thyroid function and serum biochemistry). Severe GHD is diagnosed in cases of peak GH less than 9 mU/l following a GH stimulation test. In obese patients, the diagnosis of GHD should be supported by additional tests for other hypopituitary hormone deficiencies and/or structural pituitary disease. In cases of isolated GHD, usually two GH provocation tests are performed to account for the low specificity of the test.

The annual monitoring of GH replacement therapy includes the shared care recommendations for 6-monthly outpatient visits to the endocrinology department of the local hospital, where blood tests and an annual MRI are performed, and 6-monthly visits to the general practitioner (GP) surgery, where blood tests as well as blood pressure and weight monitoring are performed.[31]

Modelling incorporates current drug dose recommendations, and uses the literature to estimate the average age at the start of treatment and life expectancy. Costs are estimated under three scenarios, which describe key combinations of factors that influence the cost of treatment. The scenarios are set out in *Table 5*.

Parameters and data

Table 4 describes the main model parameters, the values associated with each and the source of these values.[3,31,46–49]

TABLE 4 *Model parameters and data*

Parameter	Value and source
Average age at start of treatment	CO-GHD: 18 years (expert opinion) AO-GHD: 40 years (most trials report mean age above 40 years, even when consecutive patients are recruited)
Life expectancy in England and Wales	Males, 75 years (Office of National Statistics, mid-1999 estimate) Females, 79 years (Office of National Statistics, mid-1999 estimate)
Sex of patients with GHD	CO-GHD: 50% male (modeller's assumption) AO-GHD: 50% male (modeller's assumption)
Percentage who continue treatment after 6 months	80%[31]
Starting GH dose	0.2 mg/day[3]
Median and range of maintenance GH dose (mg/day)	Median dose, 0.4 mg/day[31] Range, 0.13–1.2 mg/day[31]
Cost data (2000 values) GH drug cost (Genotropin, Humatrope, Norditropin, Saizen, Zomacton)	£20.82–23.42 per mg[46]
Outpatient visit (generic)	£68 per visit[47]
Day admission (generic)	£70 per day[47]
G grade nurse	£33 per hour[47] for E grade, adjusted based on midpoint differences at Southampton University Hospitals Trust
X-ray (BMD)	£12 per test[48]
MRI (skull)	£126 per procedure[48]
Blood test (thyroid function, serum biochemistry, glucose, HbA_{1C}, IGF)	£4 per test[48]
GH provocation test (insulin, glucagon)	£219 per test (six blood tests and 6 hours of nurse's time (G grade); a day case accounted for separately (expert opinion)
Discounting rate for costs	6.0% (NICE)[49]

BMD, bone mineral density; NICE, National Institute for Clinical Excellence

TABLE 5 *Scenarios for cost model*

Scenario	Description
A	Annual cost of GH replacement (first and subsequent years) was based on the health services provided for treatment monitoring and a 20% chance of discontinuing treatment after 6 months. Present-value lifelong cost of GH replacement for the average patient with CO-GHD or AO-GHD assumes the annual cost of subsequent years recurs over the patient's lifetime and was estimated using the baseline discount rate
B	Annual cost of GH replacement in adults with AO-GHD was based on the incremental health services associated with diagnosis and monitoring of GHD
C	First-year annual cost of GH replacement, with first 3 months of GH treatment borne by the pharmaceutical sector

Model assumptions

The main model assumptions are specified as follows.

- Discontinuation of treatment was assumed to take place after 6 months of GH replacement, and base case value is 20%. Scenario analysis allowed for 0%, 40% and 60% discontinuation rates.
- Length of treatment was modelled from the average age at the start of treatment for CO-GHD and AO-GHD until death, based on age-adjusted life expectancy for England and Wales.
- Minimum current *British National Formulary* (*BNF*) price listed for somatropin was used in the base case,[46] and additional value-added tax (VAT) charges were not calculated.

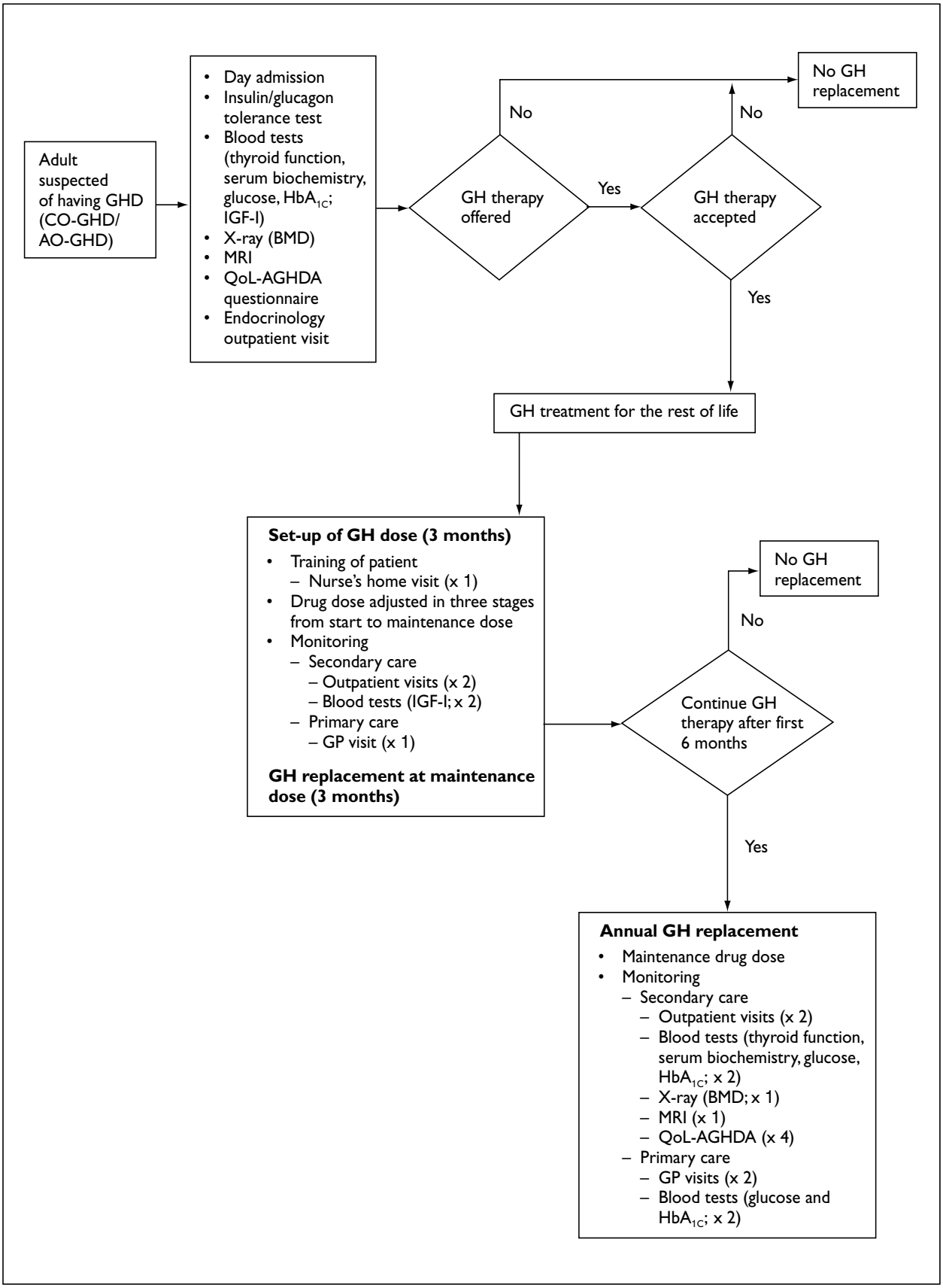

FIGURE 10 *Expected treatment pathway for patients with GHD*

- Shared care arrangements between specialists and GPs were advised by the Society for Endocrinology,[3] and it was assumed treatment monitoring took place in secondary and primary care.
- Either the patient's GP or specialist can prescribe somatropin. Prescribing practice varies across England and Wales, but was assumed not to make a difference to the overall cost of prescribing.
- If it was not possible to use generalisable costs (i.e. for the costs of diagnostic procedures), local health service costs were used. This may bias cost estimates but can be easily substituted if and when data that are more reliable become available.

Results

The average costs of diagnosis and of annual and lifelong GH replacement treatment for scenarios A, B and C are provided in *Table 6* (year 2000 prices).

The present value of lifetime costs of GH replacement under the base case assumptions was estimated to be about £42,000 for AO-GHD and £45,400 for CO-GHD (scenario A). The cost difference between the two conditions was explained by different treatment durations.

The main cost component was the cost of GH, which accounted for 87% of the total cost and 89% of the annual treatment cost on average maintenance dose.

The estimated lifetime treatment costs of GH replacement in patients with AO-GHD decreased by £2364 if only incremental health services were considered (scenario B). These differences were a small proportion of the full annual treatment cost (scenario A) and accounted for about £265 from the first-year cost and £130 annually thereafter.

Under scenario C, the cost of the drug was borne by the pharmaceutical company for the first 3 months of treatment. This reduced the average NHS cost per patient started on GH treatment by £562 for the first year for both conditions.

The sensitivity of cost estimates was analysed using one-way sensitivity analyses, and the results are presented in *Table 7*.

GHD is a chronic condition, and lifelong therapy is necessary in order to maintain the beneficial effects of treatment. Thus, not surprisingly, the length of treatment and discount rate were the two most important factors affecting cost.

TABLE 6 *Costs of GH replacement in GH-deficient adults*

	Scenario		
	A	**B**	**C**
CO-GHD			
Diagnostic cost	£515		£515
First year of treatment			
– Total cost	£3,086		£2,524
– GH cost	£2,402		£1,840
Annual GH replacement at maintenance dose			
– Total cost	£2,739		£2,739
– GH cost	£2,432		£2,432
Lifelong treatment			
– Present-value total cost	£45,364		£44,802
– Present-value GH cost	£39,480		£41,320
AO-GHD			
Diagnostic cost	£515	£301	£515
First year of treatment			
– Total cost	£3,086	£2,822	£2,524
– GH cost	£2,402	£2,402	£1,840
Annual GH replacement at maintenance dose			
– Total cost	£2,739	£2,605	£2,739
– GH cost	£2,432	£2,432	£2,432
Lifelong treatment			
– Present-value total cost	£42,034	£39,670	£41,472
– Present-value GH cost	£36,524	£36,524	£38,364

TABLE 7 *One-way sensitivity analysis*

	Range		CO-GHD		AO-GHD	
	Low	High	Minimum cost estimate	Maximum cost estimate	Minimum cost estimate	Maximum cost estimate
1. Length of GH replacement (years)	5	60	£13,010	£45,398	£13,010	£45,398
2. Discount rate for costs	0%	10%	£28,201	£163,900	£27,727	£103,643
3. Maintenance GH dose (mg/day)	0.1	1.2				
Total cost			£15,895	£123,950	£14,782	£114,708
Annual cost (maintenance GH dose)			£915	£7,603	£915	£7,603
4. Continuance of treatment	20%	100%				
Total cost			£12,575	£56,294	£11,743	£52,132
Annual cost (maintenance GH dose)			£685	£3,424	£685	£3,424
5. GH cost	£20.82	£23.42				
Total cost			£45,364	£50,294	£42,034	£46,595
Annual cost (maintenance GH dose)			£2,739	£3,043	£2,739	£3,043

The annual cost of GH replacement at maintenance dose was £2739 per patient started on GH therapy for each condition (80% continue after the first 6 months) and increased to £3424 per annum, assuming 100% of patients continued treatment. Under the most optimistic assumption that 100% of patients continue treatment after the first 6 months, present-value total cost was £56,294 for CO-GHD (compared with £45,364 under 80% continuance) and £52,132 for AO-GHD (compared with £42,034 under 80% continuance). Increasing rates of discontinuation of GH replacement therapy decreased the average cost per patient (but, of course, resulted in no benefits for those patients discontinuing therapy).

The dose of GH is an important cost factor. The base case (scenario A) was based on typical prescribing practice (i.e. GH dose, 0.4 mg/day). However, this dose can vary from 0.13 to 1.2 mg/day, and thus annual treatment cost varied from £915 to £7603 per patient (assuming 80% continuance of therapy after first 6 months) or £1144 to £9503 (if 100% continuance was assumed).

In particular, and of importance to NHS decision-makers, is the impact of a small change in the cost of GH. In this case, an apparently small difference of £2.60 per mg, which represented the difference between the least and most expensive brand price listed in the *BNF*, increased the annual and total cost of GH replacement for each condition by 11%. In practice, local NHS payers may negotiate an actual price lower than the *BNF* price, but there was no reliable price data to inform the analysis. Because it was not possible to ascertain the true drug price locally, local variations in the value of this parameter could have a significant impact on cost and cost-effectiveness.

The cost model of GH replacement in adults reported so far analysed direct treatment costs. A 6-month RCT of GH replacement[20] reported that the treated patients had significantly lower rates of hospitalisations compared with non-GH-treated patients (7% versus 14.1%, respectively, at 6 months). Based on this result and an average length of stay of 7.7 days (based on NHS Hospital Inpatient Data, 1999/2000) and a cost of £223 per inpatient day,[47] the cost saving due to prevented hospitalisations for GH-treated patients was estimated at £122 annually, or £1981 (CO-GHD) and £1833 (AO-GHD) for lifelong GH replacement. No change was seen in the number of visits to physicians in this study. Taking into account these savings for the NHS, the total incremental cost of full GH treatment (100% continuation with treatment) from the NHS and Personal Social Services perspective was £54,313 for CO-GHD and £50,299 for AO-GHD, or £43,755 (CO-GHD) and £40,544 (AO-GHD) when continuation with therapy is 80%. The analysis of the cost of treatment with savings from decreased rates of hospitalisation should be considered tentative evidence because the only data available were the hospitalisation rates. No data on the type of hospitalisation or length of stay have been reported, and groups were not analysed for comparativeness with respect to GHD condition and health status.

The same study[20] reported 4.45 fewer sick-leave days at 6 months for GH-treated patients compared with non-treated patients. Annually, this difference corresponds to 8.9 fewer sick-leave days or £738 savings from productivity loss (based on a gross income of £10.36 per hour [Office of National Statistics, 2000], and an 8-hour work day).

Budgetary impact

The results from the analysis of the budgetary impact are presented in *Table 8*. The analysis is based on total lifetime costs of GH-deficient patients who started treatment, with 20% discontinuation of treatment after the first 6 months. Two types of analyses are presented: (1) excluding savings from prevented hospitalisations and lifetime cost of GH treatment of £45,364 for CO-GHD and £42,034 for AO-GHD and (2) including savings from prevented hospitalisations and lifetime cost of GH treatment of £43,755 for CO-GHD and £40,544 for AO-GHD.

Summary of economic analysis

- There were no suitable published cost-effectiveness or cost–utility studies or models available to inform NHS decision-making.
- No suitable effectiveness measure to inform the economic analysis was identified.
- Three cost studies were identified, and simple and transparent cost models for AO- and CO-GHD were built to update previous cost analysis and to allow more scenarios and sensitivity analysis to be performed. These models can be re-evaluated in time if better data become available.
- GH replacement in adults costs £3424 annually at average maintenance GH dose or between £42,000 (AO-GHD) and £45,400 (CO-GHD) for full lifelong therapy (without the savings from prevented hospitalisations) or between £43,800 (CO-GHD) and £40,500 (AO-GHD) (with the savings from prevented hospitalisations). The results assume a 20% rate of discontinuation of GH replacement after 6-month treatment.
- Drug cost is the single most important factor in determining treatment costs. A small change in the price of somatropin can expect to significantly alter treatment costs, and thus any potential for small price reductions could still result in reasonable cost savings for the NHS. The price at the local level could significantly differ from the *BNF* list price, but there are no reliable data to inform the analysis.
- There is a small difference in the relative total cost of AO-GHD versus CO-GHD due to the different overall length of GH therapy (different average age at diagnosis).
- There is a need for better evidence on the impact of GH replacement on the length and QoL of GH-deficient patients before it is possible to estimate a cost per QALY for each condition.

TABLE 8 *Estimate of the budgetary impact of GH replacement in GH-deficient adults in England and Wales*

	Prevalence		Incidence*	
	Population size	**GH treatment cost**	**Population size**	**GH treatment cost**
Without savings from prevented hospitalisations				
AO-GHD	4200	£176,544,404	420	£17,654,440
CO-GHD	4200	£190,530,117	79	£3,598,395
With savings from prevented hospitalisations				
AO-GHD	4200	£170,284,482	420	£17,028,448
CO-GHD	4200	£183,772,183	79	£3,470,763

* *Incidence of CO-GHD in adulthood is based on an incidence of CO-GHD of 1 in 5000 births and the assumption that 60% will continue to be GH-deficient in adulthood*

Chapter 5

Management of transition patients

The major clinical issues in the management of transition patients are:

- determining whether ongoing GHD exists and will need treatment
- recommending the continuation or interruption of GH therapy (if a patient chooses to discontinue treatment, there will be issues around the need for monitoring and the possibility that GH treatment will have to be reinstituted).

Between 25% and 75% of transition patients with isolated idiopathic GHD exhibit normal values on provocation retesting. Most patients with GHD (with or without other pituitary hormone deficiencies) associated with known congenital syndromes, hypothalamic–pituitary tumours or other acquired causes of hypopituitarism will retest as having ongoing GHD, as will nearly all transition patients with multiple pituitary hormone deficiencies. However, the ideal appropriate test for redetermination of GHD in adulthood has not been defined.

On retesting positively for GHD at final height, an adolescent may continue with GH replacement without interruption or have a period of GH discontinuation. Opinion is still divided over which patients should continue therapy seamlessly and in which patients it may be reasonable to undertake a period of careful clinical assessment. The optimum dosing strategy has not been defined but is likely to involve gradual downward titration from the childhood dose to the adult dose.

There is little information about QoL factors in transition patients. One RCT[50] has considered the continuation of GH replacement in GH-deficient patients during transition from childhood to adulthood after cessation of linear growth, when discontinuation of GH therapy is usually considered, and reported QoL. The study was a double-blind, placebo-controlled trial of 1 year, followed by an open phase of 1 year when all patients received GH. All patients had received GH replacement for 3 years prior to the study. QoL was assessed using the GHQ. After 12 months in either group, there was no effect on total score or subscores of general illness, somatic symptoms, sleep disturbance, social dysfunction, anxiety and dysphoria, or severe depression, according to the GHQ. After 24 months, the placebo-treated group tended to have a lower total GHQ score, indicating a better QoL when GH was resumed, although results were not statistically significant (baseline, 45.1 ± 4.7; 12 months, 50.5 ± 6.9 ($p = 0.5$); 24 months, 38.3 ± 3.5 ($p = 0.07$).

Chapter 6

Research in progress

A number of research projects assessing GH replacement in adults are currently underway. Ongoing studies include the following.

- "Does growth hormone replacement correct cardiac autonomic dysfunction, improve cardiac structural and functional abnormalities and improve quality of life in adults with growth hormone deficiency?" This controlled trial involves a questionnaire or interviews. The funder is the Child Growth Foundation, London, and the end date is 30 September 2002.
- "Kabi International Metabolic Study (KIMS): growth hormone replacement therapy in adult patients with growth hormone deficiency: a study." The aim of this study is to assess the long-term risks and benefits of GH replacement in GH-deficient adults. The funder is not known, and the end date is 31 December 2015.
- A protocol for a review with the Cochrane Metabolic and Endocrine Group entitled, "Substitution therapy with recombinant human growth hormone for adult growth hormone deficiency". Sesmilo G, Ortega E, Webb SM. This review is expected to be published in Issue 2, 2003, of The Cochrane Library.

Chapter 7

Implications for other parties

Implications for the NHS

It is estimated that about 60% of adults with GHD do not receive GH replacement therapy. Some of these patients will not have clinical need, but others may not be receiving therapy that could be beneficial. Extending the uptake of GH therapy to all those with clinical need would have a significant budgetary impact, although not all individuals offered GH replacement therapy will necessarily accept treatment.

Also to be considered is the financial impact on the welfare state and patients, if GH treatment allows GH-deficient patients to return to work.

Implications for caregivers

GHD, whether isolated or part of a broader health problem, is a chronic disease that will have major effects on patients' families and caregivers.

Factors relevant to NHS policy

Mechanisms for funding GH prescriptions vary considerably among health authorities. Uniform policy on prescribing GH would help to alleviate regional differences in prescribing.

GH replacement, when given in the correct doses, is not a drug therapy in the conventional sense because it is seeking to restore normal physiology, but it must be closely monitored. Many endocrinologists are of the opinion that to not treat GH-deficient patients who have symptoms is unethical.

Chapter 8
Discussion

Statement of principal findings

Seventeen RCTs considering the effect of GH on QoL in adults are included in the review. The RCTs were of variable quality, and most studies included both AO- and CO-GHD. Various QoL outcome measures were reported.

One trial reported a statistically significant improvement in the GH-treated group, based on the NHP overall score. Analysis of the individual dimensions of the NHP demonstrated statistically significant improvements in the GH replacement group, compared with the control group, on the pain, emotional reactions and sleep subscales. Meta-analysis showed differences in favour of GH, with statistically significant results for the social isolation subscale of the NHP.

Meta-analysis of trials reporting the HDS and PGWB both found differences in favour of GH treatment, but results were not statistically significant. There were a large number of other non-significant results.

Adverse event data show that there was a 10–25% increase in reports of oedema and a 10–17% increase in reports of arthralgia in GH-treated groups compared with control groups.

No suitable economic evaluations of GH in adults were found. There were no available data to estimate a cost per unit of effect or cost per QALY. Cost models based on the current practice in England and Wales were built. GH replacement in adults costs £3424 annually at average maintenance GH dose or between £42,000 (AO-GHD) and £45,400 (CO-GHD) for full lifelong therapy.

Strengths and limitations of the review

The review has certain strengths, which include the following.

- It is independent of any vested interest.
- The review brings together the evidence on the effectiveness of GH replacement for adults with GHD and an economic model, applying consistent methods of critical appraisal, presentation and transparency.
- The review was guided by the principles for undertaking a systematic review. Prior to undertaking the review, the methods of the review were set out in a research protocol (appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.
- The review of clinical effectiveness relied upon evidence from RCTs that reported QoL.
- The developed cost models take the NHS and Personal Social Services perspective and estimate the full treatment costs depending on the main treatment parameters. The results can be easily revised as new evidence becomes available.

In contrast, there were certain limitations placed upon the review.

- Synthesis of the included studies was mainly through narrative review. Due to differences in the design, duration, outcome measures and reporting of studies, meta-analysis was limited to only four outcome scales (GHQ, NHP, HDS and PGWB) and was based on two, four, two and two trials, respectively. Consequently, some trials have been reported several times in the review, in that they contribute to several meta-analyses depending on outcomes used.
- The quality of the RCTs was assessed using the Jadad scale.[5] Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/drop-outs, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawal/drop-out). It has also been pointed out that the Jadad scale "gives more weight to the quality of reporting than to actual methodological quality".[51]
- It is possible that, because of the focus of the review (i.e. QoL), despite robust methods, it

failed to detect some of the favourable beneficial effects of GH treatment. A wide range of benefits are claimed for GH treatment in GH-deficient adults, including improvements in psychological well-being and QoL, BMD, body composition and cardiovascular risk profile. Clearly, each of these might contribute in complementary ways, in the short term and in the long term, to QoL and/or length of life – and so contribute to QALYs. As explained on page 1, it was decided at the outset that the review would not look at this full range of possible outcomes but would concentrate on psychological well-being/QoL. This decision was made for three reasons.

1. QoL is the final common pathway of short-term patient benefit for all the intermediate outcomes, as previously described.
2. The major indication in the UK for a trial of GH treatment in GH-deficient adults is often impaired QoL.*
3. The nature of the evidence available for most of these outcomes would have necessitated the construction of a complex and opaque model.

It would of course be possible to produce a fuller, more complex review and model, in order to combine the full range of outcomes and to generate a more inclusive estimate of effectiveness and therefore cost-effectiveness. It will be very important for anyone producing such a model to construct it in a transparent manner, to populate it with plausible parameters taking due account of uncertainty, to have it independently validated, and to ensure that it is available for regular update, as and when new data become available.

Other issues

- Various QoL instruments have been used in the reported studies. Most are generic scales (e.g. the NHP and GHQ) incorporating different dimensions, but these scales may not be appropriate for measuring the effect of GH treatment. For example, the NHP has been criticised because it detects only the severe end of ill health, and therefore most people score zero on most dimensions.[52] It is unlikely to be sensitive to small changes in health status and may result in an underestimate of the effectiveness of the intervention and inconsistent findings in trials.
- It is difficult to interpret the meaningfulness of change scores of QoL profiles such as these for adults with GHD, with statistical significance not equating to clinical significance. Some authors give a rule of thumb that a change of one-third of a standard deviation is meaningful to the patient, but this is dependent on the sensitivity of the outcome measure and on its scaling properties.
- Problems with interpretation of generic scales have led to the development of an instrument specific to GHD in adults (QoL-AGHDA) because it provides a uni-dimensional index of QoL specific to adult GHD. However, it has not been used extensively in trials to date.
- Another problem with the instruments used to measure QoL is that they may fail to pick up improvement in QoL due to reduced hospitalisations and sick-leave rate.
- The RCT is the study of choice for the review, based on the need for a placebo-controlled group in a randomised trial in order to abolish potential confounding effects. This is important in the case of GHD in adults because there is good evidence from a number of the trials of a marked placebo effect, with patients in the placebo group demonstrating improvements in QoL.
- Also, the issue of common side-effects, specific to GH, is important in potentially unblinding patients in trials of GH, with the consequent possibility of bias. Side-effects are more frequent at higher doses and are less common when the dose is carefully titrated from a lower starting dose, but this titration was not always performed in the reported trials, with resulting unblinding problems.
- An important issue that could not be explored within the context of the review is which patients with GHD may benefit most from GH replacement in terms of QoL. It has been suggested that psychological improvements are "particularly evident in those patients with the greatest deficit prior to treatment".†

* Shalet SM. Growth hormone (GH) replacement is not justified for all adults with GH deficiency. *J Clin Endocrinol Metab* 2000;**85**:937–9.

† Society for Endocrinology and Royal College of Physicians. Health Technology Appraisal of human growth hormone replacement in adults. Submission to the National Institute for Clinical Excellence. Bristol, UK: Society for Endocrinology; and London: Royal College of Physicians; August 2001.

- It should be noted that the intervention and control groups in a number of the trials included in the review have poor baseline equivalence. Also, there are differences in baseline NHP scores between studies. These factors have an impact on interpretation of results and generalisability.
- It has not been possible to explore heterogeneity within the trials or to undertake subgroup analysis.
- Sample size and power calculations were not always mentioned in the reporting of trials included in the review, and it is possible that some RCTs were underpowered to detect differences. There are also issues about whether the changes observed in outcome measures are greater than test/retest variability.
- None of the trials were in patients over the age of 74 years. Current recommendations are not to apply an age cut-off but rather to consider older patients with hypopituitary illness for GH replacement.

Implications for research

In undertaking the review of GH replacement in adults with GHD, certain implications for research have become evident.

- There is still a need for adequately powered RCTs that are well blinded, use validated outcome measures, are of adequate duration and are stratified for relevant subgroups.
- Another area of research required is in developing methods for determining the meaning of change in QoL scores. This research would involve generating QoL preferences from scenarios using disease-specific QoL instruments, which can be rated by patients to allow QALY-type analyses to be performed. QoL scores could then be related to their utility.
- Additional research is also needed to optimise dosing strategies and the management of transition patients.

Acknowledgements

We are very grateful to the advisory panel, who provided expert advice and comments on the protocol and/or draft of this report. The members included:

Steve McKenna, PhD
Director of Research
Galen Research, Manchester

Professor David Russell-Jones
Endocrinologist
Royal Surrey County Hospital

Dr Derek Sandeman
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Professor John Wass
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Nuffield Orthopaedic Centre, Oxford.

We would also like to thank Dr Pamela Royle and Ms Liz Hodson at the Information Service, Wessex Institute for Health Research and Development.

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This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme.

The final report and any errors remain the responsibility of the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton. Ruairidh Milne and Karen Gerard are guarantors.

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Appendix 1

Review methods from the research protocol

Methods for reviewing effectiveness

The *a priori* methods used for the review are outlined below. The sources of information used are outlined in appendix 2.

Inclusion and exclusion criteria

- The intervention should be biosynthetic human GH (somatropin), which is marketed by five companies in the UK: Pharmacia, Eli Lilly, Novo Nordisk, Serono and Ferring. Respectively, the brand names of their somatropin products are: Genotropin, Humatrope, Norditropin, Saizen and Zomacton. Each product has a sequence identical to that of human GH.
- Participants were adults diagnosed with GHD and adults who were continuing treatment from childhood.
- Systematic reviews of RCTs and individual RCTs comparing GH with placebo were included in the review of effectiveness.
- The outcome for the review was QoL measures.
- It was suggested that other outcomes such as cardiovascular effects, BMD and exercise performance should be included in the review. This was considered inappropriate because these are surrogate markers, whereas QoL outcomes represent an attempt to tap into issues immediately relevant to patients. With some surrogate measures (e.g. BMD), results may indicate a change, but the patient will not feel different; with others (e.g. exercise performance), although any change will be felt by the patient, interpretation of the results is difficult.

Studies identified by the search strategy were assessed for inclusion through three stages (see *Figure 11,* appendix 2). Titles and abstracts were screened independently for inclusion by two reviewers. The full text of those studies included at this stage were examined for inclusion by two reviewers.

Additional inclusion criteria for economic evaluation were that studies must:

- be published
- be available in full (i.e. excluding abstracts), to enable adequate quality assessment because, within the scope of this review, it would not be possible to contact authors for further details
- include a comparator (or placebo)
- include both the costs and consequences (outcomes).

Data extraction strategy

Data extraction and quality assessment of the studies included in the review were undertaken independently by two reviewers. At each stage, any differences in opinion were resolved through discussion.

Quality assessment strategy

Effectiveness assessment

The quality of included RCTs was judged using Jadad criteria[5] (see appendix 3).

Methods of analysis/synthesis

- The clinical effectiveness of human GH in adults was synthesised through a narrative review with full tabulation of results of all included studies. Meta-analyses using the Cochrane Review Manager software were carried out, if practical and appropriate, in terms of heterogeneity and number of studies.
- The review includes a Quality of Reporting of Meta-analyses (QUOROM)-style flow chart of trials searched for and included.
- Observations and insights on starting/stopping rules for treatment, optimal treatment strategies and transition between paediatric and adult use, identified from the included clinical effectiveness studies, are reported.

Methods for estimating QoL, costs and cost-effectiveness

- Cost-effectiveness was assessed by a two-stage procedure. No published economic evaluation studies were found. The second stage was to adapt an existing cost-effectiveness model or to construct a new one using the best available evidence to determine cost-effectiveness in a UK setting. New models were constructed.

- In order to determine applicability and resource implications to the NHS and Personal Social Services, resources and costs were sought from published UK sources (e.g. the *BNF* or published studies) and, when appropriate and available, local NHS and Personal Social Services costs.
- Effectiveness data, in terms of the outcomes described in the above section, were extracted from published trials and used in association with the cost data to obtain measures of cost-effectiveness. From the QoL information obtained from the literature, it was not possible to calculate cost–utility estimates in terms of cost per QALY.
- The robustness of the results to the assumptions made in the model were to be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Research in progress

The following electronic databases were searched to identify research in progress: National Research Register, Medical Research Council Trials database, Early Warning System, Current Controlled Trials and the National Institutes of Health websites. The most relevant ongoing research is cited in chapter 6.

Methods of meta-analysis

Using data from included studies, a meta-analysis was performed to give an estimate of the change in QoL with GH, as opposed to placebo, in GH-deficient adults. Data required for the meta-analysis were: the mean change in QoL score with GH and the SD for this change, and the mean change in QoL score with placebo and the SD for this change. These data were frequently unavailable. It was therefore necessary to make a number of assumptions in order to pool data on QoL. These assumptions are detailed below.

1. Results were read from figures if they were not given in the text.
2. If only SEs were reported, these were converted to SDs using the formula:
   SD = SE × √group sample size.
3. Crossover trials were treated as a parallel design (i.e. mean change for all patients with GH vs mean change for all patients with placebo).
4. If male and female data were presented separately, a weighted average was taken.
5. If means were unavailable, the median was assumed to be equivalent to the mean and used instead.
6. Range was converted into SDs (assuming that 1 range was equivalent to 3 SDs).
7. If means and SDs were provided only pre- and post-treatment (or if pre- and post-treatment means and SDs were calculated), these were converted into the mean change and the SD for this mean change using the formulae presented in the Cochrane handbook, as follows.

- Mean change for treatment or placebo group (d_t or d_p) = mean estimate post-treatment – mean estimate pre-treatment.
- Variance of the change = variance pre-treatment + variance post-treatment – 2[SD pre-treatment × SD post-treatment × correlation between pre-treatment value and post-treatment value].
- The square root of the variance of the change is then used to calculate the SD for the treatment group (s_t) and the placebo group (s_p).

It was assumed that the correlation value was 0.4, which is the value suggested in the Cochrane Handbook.*

The summary statistic generated was a weighted mean difference using a fixed-effects or random-effects approach as required. Studies were weighted by the inverse of their variance (i.e. more precise estimates [from studies with larger numbers of participants] were given more weight). The meta-analysis was constructed using Review Manager software (RevMan version 4.1 for Windows; The Cochrane Collaboration, 2000, Oxford, UK).

When there was little between-study variation (i.e. the test for homogeneity resulted in a p-value > 0.1), a fixed-effects approach was adopted. When there was significant between-study variation, a random-effects approach was adopted.

* Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1.5 (updated 2002 Apr). In: The Cochrane Library. Issue 4. Oxford: Update Software; 2002.

Appendix 2

Sources of information, including databases searched and search terms

Clinical effectiveness and cost-effectiveness

The following databases were searched for published studies, recently completed studies and ongoing research.

Databases searched	Issue or dates searched	
	Clinical effectiveness search	Cost-effectiveness search
Cochrane Library (Database of Systematic Reviews and Controlled Trials Register)	2001 Issue 4	
MEDLINE (SilverPlatter®)	1985 to May 2001	May 2001
Healthstar	1975 to May 2001	
EMBASE	1989 to May 2001	May 2001
NHS Economic Evaluations Database (NHS Centre for Reviews and Dissemination, University of York)	As part of Cochrane Library	May 2001
PubMed		May 2001
Science Citation Index/ Social Sciences Citation Index		May 2001
BIOSIS		May 2001
EconLit		May 2001
PsycINFO		May 2001
Index to Scientific Proceedings		May 2001
Health Management Information Consortium		May 2001
National Library of Medicine Gateway		May 2001
National Research Register		May 2001

In addition to searching the databases, one of the key endocrinology journals, *Clinical Endocrinology*, was handsearched (both articles and conference abstracts) from 1993 to August 2000. References of all retrieved articles were searched, and relevant researchers were contacted to ensure that all eligible trials had been identified.

Industry submissions to NICE were searched for studies that met the inclusion criteria. In addition, a list of trials from industry was sought via NICE at the start of the review, as a check on the completeness of ascertainment of the review searches.

A search strategy for identifying RCTs devised by the Cochrane Collaboration was used to search MEDLINE and Healthstar. EMBASE was searched using a strategy for identifying RCTs devised by the Oxford Cairns Library.

Search terms used for GH and adult GHD were: explode "Somatropin"/ all subheadings, somatropin*, somatotropin*, somatotrophin*, growth hormone, growth hormone deficien$, GHD and adult*, genotropin*, humatrope*, norditropin*, saizen*, zomacton*, nutropin*.

Primary search terms for economics searches were:

- GH and adult GHD search terms as above
- Medical Subject Heading (MeSH) trees: "Economics", "Costs-and-Cost-Analysis", "Economics-Dental", "Economics-Hospital", "Economics-Medical", "Economics-Nursing",

"Economics-Pharmaceutical", "Fees-and-Charges", "Budgets"

- cost*, economic*, pharmacoeconomic*, price*, pricing, quality adjusted life year*, qaly*, willingness to pay, conjoint analys*, health measurement questionnaire, quality near life, ihql, wellbeing, well-being, qwb, health utilit* ind*, multiattribute* or multi attribute* or multi-attribute*, health ind*, utilit* analys*, classification near2 illness state*, 12d,15d, euroqol* or eq-5d or eq 5d or eq5d, rating scale*, visual analog*, persontradeoff or (person tradeoff) or (person trade off) or (person trade*), (health near2 stat*) or (health-status) or (health near2 utilit*), standard gamble*, timetradeoff or (time tradeoff) or (time trade off) or (time trade*)

Searches were restricted to English.

Full search strategies for economics searches are available upon request.

The process of identifying and including studies for the assessment of effectiveness is illustrated in *Figure 11*. The primary reason for excluding studies was that they did not meet the inclusion criteria (e.g. they were not RCTs or did not include the outcome of interest). A list of studies excluded after retrieval of full copies can be found in appendix 4.

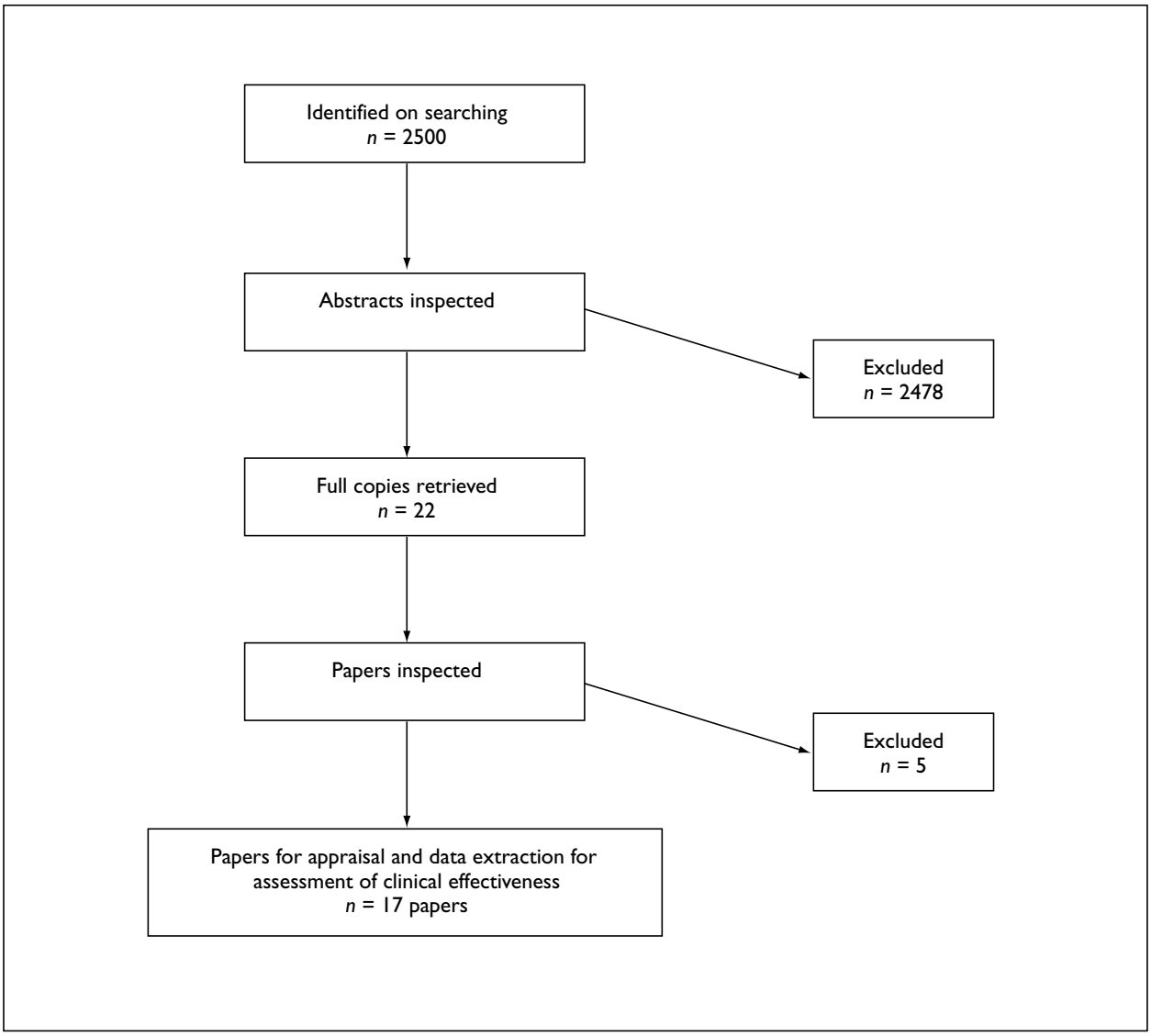

FIGURE 11 *Flowchart of identification and inclusion of effectiveness studies from the initial search*

Appendix 3

Quality assessment for RCTs (Jadad quality score)[5]

Questions to assess the likelihood of bias

Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?
Was the study described as double-blind?
Was there a description of withdrawals and drop-outs?

Scoring the items

Either give a score of 1 point for each 'yes' or 0 points for each 'no' There are no in-between marks.

Give 1 additional point if:

- for question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.) and/or
- if for question 2, the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

- for question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) and/or
- for question 2, the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy).

Guidelines for assessment

1. Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding

A study must be regarded as double-blind if the word 'double-blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and drop-outs

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 4

Excluded studies

The reasons for study exclusion are provided in brackets.

Bronstein MD, Musolino NR, Cunha NM, de Novaes Soares C, Caires MA, Rosenthal MC, *et al.* Impact of treatment with growth hormone on the psychological and somatic profile of adults with growth hormone deficiency. *Endocrinol Metab* 1997;**4**(Suppl B):167.
[Duplicate publication.]

Davies JS, Obuobie K, Smith J, Rees DA, Furlong A, Davies N, *et al.* A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. *Clin Endocrinol (Oxf)* 2000;**52**:295–303.
[Non-RCT.]

Mardh G, Lundin K, Borg G, Jonsson B, Lindeberg A. Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: combined data from 12 European placebo-controlled clinical trials. *Endocrinol Metab* 1994;**1**:43–9.
[Non-systematic review.]

McGauley GA, Cuneo RC, Salomon F, Sonksen PH. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. *Horm Res* 1990;**33**(Suppl 4):52–4.
[Duplicate publication.]

Rekers-Mombarg LT, Busschbach JJ, Massa GG, Dicke J, Wit JM. Quality of life of young adults with idiopathic short stature: effect of growth hormone treatment. Dutch Growth Hormone Working Group. *Acta Paediatr* 1998;**87**:865–70.
[Non-RCT.]

Appendix 5

QoL outcome measurement scales used in trials of GH in adults

Name of scale	Measure and scoring	Validity and reliability
Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) McKenna *et al.*, 1999[25]	• Condition-specific QoL measure, with 25 items • Includes work, tiredness, social relationships, concentration and emotions • Questions answered yes or no, with 1 point for every yes • Questions all in one direction, thus the higher the score, the lower the QoL	• Initial reliability by test–retest > 0.85 and Cronbach's alpha > 0.88 • Validity correlations between this measure and PGWB > 0.74, and correlations with NHP dimensions from 0.26 to 0.74 McKenna *et al.*, 1999[25]
Beck Depression Inventory (BDI) Beck *et al.*, 1961[53]	• Specific scale for depression • Widely used since 1961 • Contains 21 items, each with 4 response choices ranked in order of severity • Measures include sadness, dissatisfaction, guilt, self-dislike, irritability, body-image distortion and insomnia	• Scale correlates well with clinicians' ratings of severity of depression and with other depression scales (> 0.70) • Used successfully in general population, although mostly focused on psychiatric populations • Reliability (test–retest > 0.73) and validity good Bowling, 1995[54]
Comprehensive Psychopathological Rating Scale (CPRS) Asberg *et al.*, 1978[55]	• Self-assessment scale for psychiatric symptoms • 65 items, with subscales for depression, schizophrenia, obsessive–compulsive disorder, neurasthenic syndromes and mental distress in connection with physical illness • Can also be used by clinicians	• Authors describe good validity when correlated with the HDS • Demonstrated to differentiate well between depressed and anxious patients • Validity of some of the available international versions also good Montgomery & Asberg, 1979[56]
Disease-Specific Questionnaire (DSQ) Holmes *et al.*, 1995[57]	• Questionnaire developed for assessing QoL in GH-deficient patients • Based on two qualitative studies • Development paper for QoL-AGHDA	• No further details found by searches of databases
Growth Hormone Deficiency Questionnaire (GHDQ) Cuneo *et al.*, 1998[11]	• Questionnaire developed for Cuneo trial and based on group discussions with adults with GHD, regarding mood, energy and sleep • 30 questions, each answered on a visual analogue scale	• Unpublished data suggest that the GHDQ has been validated in normal individuals and used in a pilot study with GH-deficient adults • No further details found on searches of databases
General Health Questionnaire (GHQ) Goldberg, 1972[58]	• Screening questionnaire for detecting independently verifiable forms of psychiatric illness • Purely a measure of state • Originally 60 items (shorter versions available), each with 4 response choices ranked in order of severity	• Most widely applied self-completion measure of psychiatric disturbance in the UK • Correlates well with psychiatric diagnoses of morbidity and depression • GHQ-30 demonstrated to have good criterion validity, content validity, construct validity and predictive validity • Cross-cultural validation also shown • Reliability also good (split-half correlation of 0.95) • Validity of GHQ-12 also good Bowling, 1995[54]

continued

Name of scale	Measure and scoring	Validity and reliability
Hospital Anxiety and Depression Scale (HADS) Zigmond & Snaith, 1983[59]	• Brief assessment of anxiety and depression, which can be used as a screening tool • A measure of state, with 14 items rated on a 4-point scale • Scored 0–3 or 3–0 • Using psychiatric diagnosis as a gold standard, ratings of 11+ generally used as the cut-off for above normal	• High correlation with clinical psychiatric assessments and also other inventories • HADS gives meaningful results as a screening tool (sensitivity of 88%) compared to the structured clinical interview for the DSM-III • Internal consistency shown to be fairly high, and can differentiate between anxiety and depression well • Some work on validity undertaken, but not enough • Test–retest reliability good Bowling, 1997[60]
Hamilton Depression Scale (HDS) Hamilton, 1960[61]	• Assesses cognitive and behavioural components of depression • Not designed to diagnose depression, but to assess severity • Individually rated by an interviewer • Contains 17 items (21 items in first version), including depressed mood, feelings of guilt, agitation, anxiety and gastrointestinal symptoms • Some items scored 0–4 (absent to severe) and others 0–2 (absent to clearly present) • Children's version also available	• Reported to have high concurrent validity, with good agreement with other scales (> 0.70) • Value depends on the skill of the interviewer, although inter-rater reliability reported to be > 0.84 • Reliability and validity good, although most testing undertaken with psychiatric populations • The total score has been shown to be a weak index of depressive syndrome severity • Widely used by investigators Bowling, 1997[60]
Hopkins Symptom Checklist (HSCL-56) See also SCL-90 Derogatis *et al*., 1974[62]	• Several scales of varying length • HSCL-56 contains items under five subscales: depression, anxiety, somatisation, obsessive–compulsive and irascibility • A measure of state • Uses a 5-point distress scale, from no distress to moderate-to-extreme distress	• Correlations of the SCL-90 with the MMPI scales range from 0.40 to 0.75 • Subscales also have had extensive testing, and the HSCL-56 is reported to have good validity and to be sensitive to treatment effects • Test–retest correlations of the HSCL-56 were > 0.75 for all subscales Bowling, 1995[54]
Impact Scale Jacoby *et al*., 1993[63]	• Used originally in epileptic patients • Measures the impact of the condition on a number of different aspects of daily life • Adapted by Wallymahmed for use in GH-deficient adults	• Evidence of test–retest reliability in region of 0.70–0.92 • Validity also said to be good, as reported by Wallymahmed and co-workers[21] • No further details found on searches of databases
Kellner Symptom Questionnaire (KSQ) Also known as the Symptom Rating Test Kellner, 1983[64]	• Evaluates the degree of psychological discomfort or lack of well-being, with four main areas: anxiety, depression, somatisation and hostility • Self-report measure (38 items) uses a numerical scale for each item, ranging from 0 to 4	• Authors validated KSQ against the HDS, with favourable levels • Test–retest reliability also good • Few other validation studies
Life Fulfilment Scale (LFS) Baker *et al*., 1994[65]	• Based on Krupinski 1980 report (reference not found) • Weighs aspects of QoL and assesses the discrepancy between their actual and desired circumstances • Divided into two subsections: personal and material fulfilment	• Baker and co-workers[65] suggest that scale has been shown to be reliable and valid • No further details found on searches of databases

continued

Name of scale	Measure and scoring	Validity and reliability
Mental Fatigue Scale (MFS) Bentall *et al.*, 1993[66]	• Brief mental fatigue scale • Developed by Bentall and colleagues[66] for patients with CFS	• Administered to normal individuals, patients with CFS, individuals who recovered from CFS and depressed patients • Found to have good internal consistency and discriminated well between patients recovered from CFS and normal individuals, but failed to discriminate between patients with CFS and depressed patients • Little work found on this scale
Minnesota Multiphasic Personality Inventory (MMPI) Dahlstrom *et al.*, 1972[67]	• Developed in 1940 • Test was revised in the early 1990s, hence its new incarnation as the MMPI-2 • Contains 567 items • Six validity scales and ten basic clinical/personality scales: hypochondriasis, depression, hysteria, psychopathic deviate, masculinity–femininity, paranoia, psychasthenia, schizophrenia, hypomania and social introversion	• Standardised questionnaire and included in this standardisation were the major ethnic/minority groups • Widely used and validated in the USA; validity outside the USA more questionable Kaye, 2001[68]
Nottingham Health Profile (NHP) Hunt, 1984[69]	• Generic health-related QoL measure • Used to evaluate perceived distress across various populations • Six dimensions (38 items): physical mobility, pain, social isolation, emotional reactions, energy, sleep • Dichotomous yes/no answers • Has a negative orientation • Score is a mean across all items	• Test–retest reliability reported to be good, particularly part 1 • Validity (tested for a number of disease states) also reported to be good • However, tends to produce skewed responses and insensitive to small improvements due to dichotomous scaling • Detects only the severe end of ill health Bowling, 1997[60]
Psychological General Well-Being (PGWB) Schedule Dupuy, 1984[70]	• Sometimes called the General Well-Being Schedule • A multi-dimensional indicator of well-being and distress • Versions with 68, 33 or 22 items available • Contains six subscales: anxiety, depressed mood, positive well-being, self-control, general health and vitality • Some questions have six response choices (scored 0–5, negative to positive), while others have a Likert-type scale (0–10, 'not concerned' to 'very concerned')	• Population norms provided • Validity reported in a number of studies to be good for internal consistency and for discriminability with non-patients • Some cross-cultural testing undertaken and shown to be good • Test–retest reliability also good on average, but can fluctuate Bowling, 1997[60]
Profile of Mood States (POMS) McNair *et al.*, 1971[71]	• Developed to assess mood in psychiatric outpatients • A measure of state • Contains 65 items with six dimensions: tension–anxiety, depression–dejection, anger–hostility, vigour–activity, fatigue–inertia and confusion–bewilderment • Rated on a 5-point intensity scale (0–4, 'not at all' to 'extremely') • Shorter and longer versions also exist	• Norms available for some patient groups (e.g. patients with cancer) • Overall validity shown to be good, although less on some dimensions (e.g. energy–fatigue) • Test–retest reliability good • Widely used test • Does not check for social desirability Bowling, 1995[54]

continued

Name of scale	Measure and scoring	Validity and reliability
Schedule for Affective Disorders and Schizophrenia (SADS) Endicott & Spitzer, 1978[72]	• Semi-structured interview	• Reported to have good validity and excellent test–retest reliability over short test periods Bowling, 1995[54]
Social Adjustment Scale (SAS) Weisman & Bothwell, 1976[73]	• Assesses interpersonal relationships in terms of feelings, satisfaction, friction and performance • Interviewer or self-report measures available • A measure of state, based on previous fortnight • Contains 54 questions covering six areas of functioning: work, leisure, extended family, marital roles, parent role and family unit • Either 5- or 6-point response scales are used, generating a mean score based on the number of items • Also available for children and severely mentally ill individuals, and for life-time measures	• Validity correlations with other depression scales range from weak to high • Test–retest reliability generally high • Norms available for hospitalised schizophrenic patients Bowling, 1995[54]
Symptom Checklist-90 (SCL-90) (later version of HSCL-56) Derogatis *et al*., 1974[62]	• Brief self-report inventory designed as a screening tool for a broad range of psychological problems and symptoms of psychopathology • Contains 90 items with 5-point rating scales and with nine primary symptom dimensions: somatisation, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism	• Shows good reliability and validity • Normalised in a number of groups: adult non-patients, adult psychiatric outpatients, adult psychiatric inpatients and adolescent non-patients • Some validation in British psychiatric patients, although it has been suggested that it may need to be supplemented with information about psychiatric history National Computer Systems, 2001[74]
Self-Esteem Scale (SES) Rosenberg, 1965[75]	• Self-report measure of self-esteem • Ten items reported on a 4-point continuum on a Likert scale • No agreement over the method of scoring: some score dichotomously and others use a summing scale	• Widely used • Shown to have strong convergent validity for men and women, different ethnic groups and dieting-disordered patients • Some work performed in other cultures • Reports of validity and reliability require further testing Bowling, 1997[60]
Sjoberg Mood Questionnaire (SMQ) Sjoberg *et al*., 1979[76]	• Measures activity, social orientation, control, extraversion, calmness and pleasantness	• No further details found on searches of databases
State–Trait Anxiety Inventory (STAI) Speilberger *et al*., 1983[77]	• Measures both state anxiety and trait anxiety • Consists of 20 items for each type • State anxiety is measured on a 4-point intensity scale ('not at all' to 'very much so') • Trait anxiety is rated on a 4-point frequency scale ('almost never' to 'almost always') • Self-administered, but for use only by trained psychometricians	• Construct validity correlations are between 0.52 and 0.80 • Also correlates well with other tests of personality, and distinguishes well between normal adults and different groups of psychiatric patients • Test–retest reliability showed stability from 1 hour to 104 days Bowling, 1995[54]

DSM, Diagnostic and Statistical Manual of Mental Disorders; CFS, chronic fatigue syndrome

Appendix 6

Summary of RCTs of effectiveness of GH in adults with GHD

Reference and design	Intervention	Participants	Outcome measures
Attanasio *et al.*, 1997[6] (UK, The Netherlands, Denmark, Sweden and Germany) Type of trial: Parallel Length of follow-up: 6 months Jadad score: 2/5	Name of GH: Humatrope Administration timing and place: Subcutaneously each day Dose: 6.25 µg/kg/day for first 4 weeks, then increased to maximum of 12.5 µg/kg/day for 6 months Did any patients receive GH before trial?: Yes, those with CO-GHD. No GH treatment in previous 2 years Other hormone replacements: Replacement therapy with cortisol, thyroxine, sex steroids and vasopressin had to be stable for at least 6 months before start of study	Total number of participants: 173 patients Isolated or multiple deficiencies: 7 patients with adult-onset deficiency had GHD, 19 patients with child-onset deficiency had GHD AO- or CO-GHD: 99 patients with AO-GHD, 74 patients with CO-GHD Severity of GHD: Peak serum GH level < 5 µg/l in a standard stimulation test (arginine, insulin tolerance, clonidine, also GH-releasing hormone, L-dopa and glucagon) Sex: CO-GHD, 55 men, 19 women; AO-GHD, 61 men, 38 women Age (mean ± SD): CO-GHD, 28.8 ± 8 years; AO-GHD, 43.5 ± 10 years Inclusion criteria: Patients with hypertension excluded	QoL scale used: NHP

Results

- Qualitative description of results
- Changes in NHP scores showed significant improvements in the placebo as well as the GH-treated patients in both groups. However, the GH treatment effect was significantly different from placebo for social isolation and physical mobility domains in AO-GHD patients but not CO-GHD patients

Comments

Methodological comments

- Randomisation method: Not stated
- Baseline characteristics not displayed by trials arms (only by adult and child onset)
- Blinding: Stated but not described
- Compliance not discussed
- Drop-outs and withdrawals: 1 adult-onset patient and 7 child-onset patients were enrolled but not randomised. These patients were included in the baseline characteristics data but not the analysis. Baseline mean NHP scores for only 61 child-onset and 87 adult-onset patients given. No information on number of patients assessed for QoL at end of trial
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Assumed

General comments

- Conflict of interests: Work supported by Eli Lilly industries

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	0

continued

Adverse events
Withdrawals from trial*

GH group (*n* = 84)		Placebo group (*n* = 81)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Total			

* *Patients withdrawn due to adverse effects, but no indication of which group patients were in*

***Adverse events* contd**
Number of specific adverse effects

Type of adverse events	GH	Placebo
Arthralgia	14	3
Fluid retention/oedema	17	2
Paraesthesia	5	2
Hypertension	0	1
Total number of events	36	8
Total number of patients with events	Not reported	Not reported

Reference and design	Intervention	Participants	Outcome measures
Baum *et al.*, 1998[7] (USA) Type of trial: Parallel Length of follow-up: 18 months. Jadad score: 5/5	Name of GH: Nutropin Administration timing and place: Self-administered at night Dose: 10 ± 0.3 µg/kg/day; mean, 4 ± 2 µg/kg/day Did any patients receive GH before trial?: Unknown Other hormone replacements: In all except 2 patients	Total number of participants: 40 patients Isolated or multiple deficiencies: All multiple deficiencies except 2 patients AO- or CO-GHD: All with AO-GHD Severity of GHD: Peak serum GH levels < 5 µg/l in response to two pharmacological stimuli (insulin, clonidine and/or arginine) Sex: All men Age: Median, 51 years; range, 24–64 years Inclusion criteria: Normal growth and development, and a diagnosis after age 18 years of benign sellar neoplasm, pituitary apoplexy or idiopathic hypopituitarism. Patients excluded if they had a history of acromegaly, diabetes mellitus or malignancy; not receiving other replacement therapies required	QoL scales used: NHP PGWB GHQ MMPI-2

Results (at 18 months)	**GH start**	**GH end**	**Placebo start**	**Placebo end**
NHP (mean ± SE):				
Emotional reactions	7.8 ± 3.1	10.7 ± 4.9	12.0 ± 4.9	3.0 ± 1.7
Energy	18.3 ± 6.2	15.6 ± 9.1	19.3 ± 8.2	8.9 ± 5.1
Pain	3.1 ± 2.5	4.2 ± 2.9	12.5 ± 4.8	2.5 ± 1.8
Sleep	15.0 ± 5.6	8.0 ± 3.3	14.0 ± 5.1	10.7 ± 3.3
Social isolation	3.2 ± 1.7	1.3 ± 1.3	3.0 ± 2.2	0.0 ± 0.0
Physical mobility	5.3 ± 2.8	3.3 ± 1.9	10.5 ± 4.0	5.8 ± 3.0
MMPI-2 (mean ± SD):				
Hypochondriasis	52 ± 10	57 ± 9	55 ± 11	53 ± 11
Depression	55 ± 11	54 ± 6	55 ± 10	55 ± 11
Hysteria	52 ± 10	57 ± 12	55 ± 9	53 ± 10
PGWB (mean ± SD)	83 ± 13	84 ± 18	85 ± 16	86 ± 8
GHQ (mean ± SD)	37 ± 17	36 ± 19	36 ± 19	31 ± 8

• No significant difference for all scales

Comments

Methodological comments

- Randomisation method: Not given
- Baseline characteristics: Similar QoL scores, except more pain (NHP subscale) experienced in placebo group
- Patients blinded to treatment: To maintain blinding, both placebo and GH-treated patients had reduced doses
- Outcome assessors blinded to treatment: Assumed
- Compliance: Based on vial count
- Were all patients accounted for at trial conclusion?: 5 patients administered GH dropped out, and 1 patient administered placebo dropped out
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Except other replacement treatments
- No point estimates or CI given
- Changes from baseline to 18 months were compared between groups using two-tailed Student's *t*-test. For NHP, change in scores from baseline to 18 months were compared between groups using Wilcoxon tests

General comments

- Conflict of interests: Supported by grants from National Institutes of Health and Genentech
- Other: One outcome of many considered

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial

GH group (*n* = 20)		Placebo group (*n* = 20)	
Reason	**Number**	**Reason**	**Number**
Oedema	0	Oedema	0
Arthralgia	0	Arthralgia	0
Seizure (stopped anti-epileptics)	1	Pneumonia	1
Tachycardia	1		
Cerebrovascular accident	1		
"Non-medical"	2		
Total	5		1

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia	0	0
Fluid retention/oedema	2*	
Myalgia	1*	
Total number of events	3	
Total number of patients with events	3	

* *Leading to a dose reduction*

Note: Adverse effects also described in previously published paper (of first 32 participants); however, number of adverse events in first report described as 4, and in later report described as 3

Reference and design	Intervention	Participants	Outcome measures
Bengtsson *et al.*, 1993[8]	Name of GH: Humatrope	Total number of participants: 10 patients	QoL scales used: CPRS SCL-90 Psychiatric interview
(Sweden)	Administration timing and place: Subcutaneous at bedtime	Isolated or multiple deficiencies: Multiple deficiencies	
Type of trial: Crossover	Dose: 0.25–0.5 U/kg/week (0.013–0.026 mg/kg/day).	AO- or CO-GHD: All with AO-GHD	
Length of follow-up: 12 months (6 months of GH, then 6 months of placebo, and vice versa)	Dose of 0.25 U/kg/week if side-effects occurred	Severity of GHD: Mean GH concentrations < 1 mU/l measured in 48 samples collected at 30-minute intervals over a 24-hour period. With ITT, all patients had GH concentrations < 1 mU/l	
Jadad score: 4/5	Did any patients receive GH before trial?: No	Sex: 9 men and 1 woman	
	Other hormone replacements: Thyroid, adrenal and gonadal replacement therapy	Age: range, 34–58 years; mean, 46.5 years	
		Inclusion criteria: Established GHD. No more information provided	

Results

- No figures were given
- After 26 weeks of GH treatment, there was a significant change in the CPRS score: 7 patients had a decreased score, 1 patient was unchanged, and 1 patient had an increased score ($p < 0.05$)
- No significant change in SCL-90 was noted

Comments

Methodological comments

- Randomisation method: Not given
- Baseline characteristics: None of the patients suffered from serious psychiatric illness. Complaints before treatment were mainly tiredness, low energy and lack of initiative, lack of concentration, memory difficulties and irritability
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: Not given
- Drop-outs and withdrawals: 1 patient withdrawn due to oedema and atrial fibrillation, and data excluded from analysis
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Yes (not applicable)
- Analysis of variance: Investigators did not carry out a placebo versus GH analysis due to substantial carry-over effect (no washout period)

General comments

- Conflict of interests: Supported by grants from Eli Lilly and Swedish MRC
- Other: One outcome of many considered

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Adverse events

Withdrawals from trial*

GH group (n = 10)†		Placebo group (n = 10)	
Reason	**Number**	**Reason**	**Number**
Oedema	0	Oedema	0
Arthralgia	0	Arthralgia	0
Atrial fibrillation (previous oedema)	1		
Total	1		0

* *Crossover trial – did not describe adverse event data separately*
† *Crossover trial – total* n *is 10*

***Adverse events* contd**

Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia	1	
Fluid retention/oedema	3	
Swollen limb or finger	1	
Carpal tunnel syndrome	1	
Tinnitus	1	
Total number of events	7	
Total number of patients with events	6	

Reference and design	Intervention	Participants	Outcome measures
Beshyah *et al.*, 1995[9] (UK) Type of trial: Parallel, double-blind Length of follow-up: 6 months Jadad score: 3/5	Name of GH: Norditropin Administration timing and place: Daily dose, subcutaneous Dose: 0.04 (0.02–0.05) IU/kg/day. Starting dose, 0.05 IU/kg/day (to maximum of 4 IU/day). Adjusted to patient's tolerance by 25% or 50% reductions Did any patients receive GH before trial?: Not stated Other hormone replacements: Conventional replacement therapy	Total number of participants: 40 patients Isolated or multiple deficiencies: Multiple, hypopituitary AO- or CO-GHD: 32 patients with AO-GHD, 8 patients with CO-GHD Severity of GHD: Serum GH < 6 mU/l in response to insulin-induced hypoglycaemia and oral clonidine Sex: 19 men and 21 women Age: 19–67 years Inclusion criteria: Not given	QoL scales used: Self-reporting in GHQ Interview using CPRS Self-reports of general well-being

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
Median GHQ (range)	3 (0–47)	1 (0–55)	12 (0–37)	4 (0–47)
Median CPRS (range)	8 (4–34)	7 (1–23)	20 (3–31)	15 (3–23)

- GHQ did not change on GH but significantly decreased on placebo ($p < 0.05$)
- No significant change in total CPRS score in either treatment group
- General well-being: Significantly more patients receiving GH reported improved well-being (comparison based on χ^2 test)

Comments

Methodological comments

- Randomisation method: Not given
- Baseline characteristics: GHQ score was significantly higher (greater morbidity) in placebo group than GH group. CPRS score also tended to be higher, but this difference was not significant. Other characteristics (age, child-/adult-onset, body mass index) were the same
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: Not given
- Drop-outs and withdrawals: 2 patients withdrew because of adverse events; 38 patients completed the trial
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Yes
- Differences before and after treatment tested with paired *t*-test. Used Mann–Whitney *U* test and Wilcoxon test for non-normally distributed data

General comments

- Conflict of interests: Funding support by Novo Nordisk Pharmaceuticals
- Other: Differences in well-being scores at baseline a potential problem

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial

GH group (*n* = 20)		Placebo group (*n* = 20)	
Reason	**Number**	**Reason**	**Number**
Oedema	1 (no response to reduction in dose)	Oedema	0
Arthralgia	0	Arthralgia	0
Accident	1		
Total	2		0 (assumed because not stated)

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia	2	0
Fluid retention/oedema (generalised or in a specific site)	8	4
Limb or finger swelling	4	0
Carpal tunnel syndrome	2	0
Disturbed sleep pattern	2	0
General or limb ache	0	2
Dizziness	1	1
Tiredness	2	2
Vaginal bleeding	0	1
Puffy face/bloating	0	1
Total number of events	21	11
Total number of patients with events	11	7

Reference and design	Intervention	Participants	Outcome measures
Burman *et al.*, 1995[10] (Sweden) Type of trial: Crossover, double-blind Length of follow-up: 21 month (9 months of GH/placebo, 3 months of washout, 9 months of placebo/GH) Jadad score: 2/5	Name of GH: Norditropin Administration timing and place: subcutaneous at bedtime by the patient Dose: Mean daily dose was 2.4 U (1.25 U/m^2; range, 0.5–4 U) Did any patients receive GH before trial?: None Other hormone replacements: Levothyroxine, adrenal and sex steroids, desmopressin	Total number of participants: 36 patients Isolated or multiple deficiencies: All patients had total pituitary insufficiency, except for 2 patients AO- or CO-GHD: 34 patients with AO-GHD, 2 patients with CO-GHD Severity of GHD: Peak response of GH ≤ 3 µg/l during insulin-induced hypoglycaemia Sex: 15 women and 21 men Age: Mean, 46 years; range, 28–57 years Inclusion criteria: None presented	QoL scales used: HSCL-56 NHP PGWB Schedule Spouse's questionnaire

Results (at 9 months)	GH start	GH end	Placebo start	Placebo end
NHP (mean ± SD):	16.7 ± 15.7	10.4 ± 14.2	16.7 ± 15.7	14 ± 17.9
Emotional reactions	23.1 ± 25.3	12.1 ± 20.9	23.1 ± 25.3	16.5 ± 24.1
Sleep	13.4 ± 19.1	12.7 ± 21.9	13.4 ± 19.1	15.3 ± 21.6
Energy	37.1 ± 39.6	16.4 ± 24.2	37.1 ± 39.6	25.1 ± 38.6
Pain	8.7 ± 18.8	8.7 ± 16.9	8.7 ± 18.8	8.8 ± 21.7
Social isolation	9.9 ± 21.9	4.5 ± 14.6	9.9 ± 21.9	8.5 ± 19.6
Physical mobility	7.8 ± 11.2	7.7 ± 12.6	7.8 ± 11.2	9.7 ± 14.4
HSCL (mean)	89	80.2	89	84
PGWB (mean ± SD)	92 ± 15.5	97.4 ± 15.4	92 ± 15.5*	93.9 ± 16.6*

- Significant reduction in NHP energy score with both GH ($p < 0.003$) and placebo ($p < 0.04$)
- Reduction in NHP emotional reactions with GH ($p < 0.003$) and placebo (not significant)
- HSCL: Scores decreased with both GH ($p < 0.001$) and placebo ($p = 0.06$); the order of treatment influenced the results
- PGWB: Increase in well-being with GH ($p < 0.05$) and placebo (not significant)

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: Not given
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: Not given
- Were all patients accounted for at trial conclusion?: 1 patient allocated to placebo group dropped out before 3 months and was replaced
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Yes

General comments

- Conflict of interests: Funding support from Novo Nordisk Pharma
- Other: Placebo effect evident (in patients who received GH first, they did less well when receiving placebo; in patients who received placebo first, they did quite well, then did much better with GH). With NHP, 6 patients had a score of 0 at baseline and therefore could not improve

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	0
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial*

GH group (*n* = 36)		Placebo group (*n* = 36)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Compliance		Compliance	1
Total			1

* *Crossover trial – did not describe adverse event data separately*

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)†

Type of adverse effects	GH	Placebo
Arthralgia		
Fluid retention/oedema		
Total number of events		
Total number of patients with events		

† *No reports of adverse effects given*

Reference and design	Intervention	Participants	Outcome measures
Cuneo *et al.*, 1998[11] (Australia) Type of trial: Parallel Length of follow-up: 6 months Jadad score: 4/5	Name of GH: Genotropin Administration timing and place: Anterior thigh or abdomen, at patient's preference, but constant throughout study Dose: 0.125 U/kg/week for first month, 0.25 U/kg/week thereafter. Maximum of 2 U in first month, 4 U in subsequent months Did any patients receive GH before trial?: Not in last 12 months Other hormone replacements: At least 6 months beforehand	Total number of participants: 163 patients Isolated or multiple deficiencies: 21 idiopathic patients AO- or CO-GHD: About one-third of patients received GH in childhood Severity of GHD: Peak GH < 5 mU/l following insulin-induced hypoglycaemia Sex (ratio of women:men): GH group, 33:50; placebo group, 39:41 Age: GH group, 41.2 ± 1.5 years; placebo group, 39.8 ± 1.5 years; range, 17–67 years Inclusion criteria: Age between 18 and 65 years. Other deficiencies replaced for at least 6 months before trial entry. Patients excluded if they had received GH in the last 12 months, history of acromegaly, uncorrected oestrogen deficiency, active Cushing's syndrome, any acute severe illness in last 6 months, pregnancy, severe chronic liver disease, chronic renal impairment, diabetes mellitus, etc.	QoL scales used: NHP GHDQ

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
NHP (mean ± SE):				
Energy	1.03 ± 0.06	0.55 ± 0.05	1.17 ± 0.05	0.56 ± 0.04
Pain	0.77 ± 0.1	0.34 ± 0.04	0.23 ± 0.06	0.28 ± 0.05
Emotional reactions	1.38 ± 0.12	0.65 ± 0.07	0.70 ± 0.07	0.58 ± 0.05
Sleep	1.14 ± 0.07	0.85 ± 0.07	0.99 ± 0.06	0.55 ± 0.05
Social isolation	0.48 ± 0.06	0.27 ± 0.04	0.24 ± 0.03	0.31 ± 0.04
Physical mobility	0.54 ± 0.07	0.61 ± 0.06	0.38 ± 0.03	0.37 ± 0.05

- Significant treatment group × time interaction in NHP pain scores (decrease in GH group and increase in placebo group; $p = 0.47$)

Comments

Methodological comments

- Randomisation method: Computer-generated listing with equal numbers coming from the ten centres included in the study
- Similar baseline characteristics: Yes, except for duration of GHD
- Patients blinded to treatment: Because of blinding, dose changes were given to all patients
- Outcome assessors blinded to treatment: Assumed
- Compliance: Assessed by vial count and injection diary. No results given
- Drop-outs and withdrawals: 19 patients from the GH group and 11 patients from the placebo group withdrew. The primary reason for withdrawal was an adverse event for 40% of patients
- Intention-to-treat analysis: Yes
- Aside from GH treatment, were the groups treated equally?: Yes, except other replacement treatments

General comments

- Conflict of interests: Funding support from Pharmacia (Australia) Pty Ltd

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial

GH group (*n* = 83)		Placebo group (*n* = 80)	
Reason	**Number**	**Reason**	**Number**
Oedema or arthralgia	13	Oedema	
Other	6	Other	11
Total	19		11

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia/myalgia	30%	13%
Fluid retention/oedema	48%	30%
Paraesthesia and anaesthesia	12%	4%
Aggressive reactions	0	3.8%
Moniliasis	0	3.8%
Increased sweating	3.6%	0
Adrenal insufficiency	5 patients	0
Operation on pituitary tumour	1 patient	1 patient
Collapse	1 patient 2 events	0
Amaurosis fugax and chest pain	1 patient	0
Total number of events	290*	219*
Total number of patients with events	70*	60*

Note: Some data reported as percentage of incidence, and some reported as numbers of patients

?, Not clear if this value is percentage of total or percentage of numbers in study arm

* *Reported numbers; unable to calculate from data given*

Reference and design	Intervention	Participants	Outcome measures
Degerblad *et al.*, 1990[12] (Sweden) Type of trial: Double-blind cross-over Length of follow-up: 12 weeks with washout period of at least 12 weeks, then 12 weeks of alternative Jadad score: 3/5	Name of GH: Somatrem, Somatonorm Administration timing and place: 6 or 7 nights per week, depending on body weight; subcutaneous Dose: 4 IU/day; 0.5–0.6 IU/kg/week Did any patients receive GH before trial?: 5 patients received GH during some periods in their life, but not within the last 5 years Other hormone replacements: In 5 patients (cortisone acetate, thyroxine, testosterone, or oestrogen and progesterone); 1 patient also received desmopressin	Total number of participants: 6 patients Isolated or multiple deficiencies: 5 patients had panhypopituitarism, and 1 patient had isolated partial GHD AO- or CO-GHD: 5 patients with CO-GHD, 1 patient with AO-GHD Severity of GHD: With the arginine–insulin test, 4 patients showed no increase in GH concentration, and 2 patients showed a small response (0.6 and 3.4 µg/l) Sex: 3 men and 3 women Age: 20–38 years	QoL scales used: POMS questionnaire SMQ Cognitive function was assessed by psychometric tests and finger tapping test used to record motor speed

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
SMQ (mean ± SE):				
Activity	2.78 ± 0.23	2.97 ± 0.28	2.70 ± 0.20	2.60 ± 0.18
Social orientation	3.12 ± 0.13	2.92 ± 0.18	2.83 ± 0.12	2.95 ± 0.19
Control	2.77 ± 0.19	2.97 ± 0.17	2.70 ± 0.16	2.72 ± 0.19
Extraversion	2.70 ± 0.12	2.82 ± 0.11	2.67 ± 0.08	2.57 ± 0.07
Calmness	2.53 ± 0.26	2.70 ± 0.14	2.60 ± 0.13	2.42 ± 0.17
Pleasantness	2.93 ± 0.16	2.76 ± 0.28	2.55 ± 0.12	2.58 ± 0.19
POMS (mean ± SE):				
Tension	2.67 ± 0.26	2.65 ± 0.25	2.60 ± 0.21	2.77 ± 0.29
Depression	2.17 ± 0.20	1.93 ± 0.24	2.47 ± 0.42	2.55 ± 0.39
Anger	1.97 ± 0.23	2.10 ± 0.27	2.13 ± 0.39	2.50 ± 0.30
Fatigue	2.77 ± 0.24	2.50 ± 0.44	2.97 ± 0.34	2.93 ± 0.23
Confusion	2.20 ± 0.28	2.40 ± 0.35	2.73 ± 0.31	2.58 ± 0.30

- No significant difference between the results at onset and end of each treatment period, nor between the two different treatment periods in the self-reported mood scales and the cognitive tests
- Finger tapping (motor speed) was unaltered

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: Yes
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: No information given
- Were all patients accounted for at trial conclusion?: Yes
- Aside from GH treatment, were the groups treated equally?: Yes (crossover trial)
- Used *t*-test and analysis of variance for mood scales and cognitive tests

General comments

- Conflict of interests: Funding support from Karolinska Institute, Swedish Medical Research Council, Svenska Sallskapet for Medicisk Forskning, Nordisk Insulin Foundation, Magnus Bergvall Foundation and Clas Groschinskys Minnesfond. Supply of Somatonorm from KabiVitrum AB, Stockholm
- Other: Very small number of patients and short treatment period

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial[*]

GH group (*n* = 6)[†]		Placebo group (*n* = 6)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Moved away		Moved away	
Total			

[*] *Crossover trial – did not describe adverse event data separately*
[†] *Crossover trial – total* n *is 6*

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia	1	
Fluid retention/oedema	1	
Total number of events	2	
Total number of patients with events	1	

Note: 5/6 patients identified the periods with GH and placebo

Reference and design	Intervention	Participants	Outcome measures
Deijen *et al.*, 1996[13] (The Netherlands) Type of trial: Parallel, three GH dose groups and one placebo group. Dose groups combined for RCT results Length of follow-up: 6 months Jadad score: 2/5	Name of GH: Not given Administration timing and place: No information provided Dose: 1 IU/m^2, 2 IU/m^2 and 3 IU/m^2 Did any patients receive GH before trial?: Yes, all patients, but they spent 12 months pre-trial without GH Other hormone replacements: Patients with MPHD	Total number of participants: 48 patients Isolated or multiple deficiencies: 31 patients had MPHD, 17 patients had isolated GHD AO- or CO-GHD: All with CO-GHD Severity of GHD: See inclusion criteria Sex: All men Age: Mean, 26 years for patients with MPHD and 28 years for patients with isolated GHD; range, 19–37 years Inclusion criteria: Serum IGF-I concentration at least 2 SD below the age-related normal mean, peak GH < 7 μg/l in response to 100 μg of GH-releasing hormone or insulin-induced hypoglycaemia, adequate and stable substitution treatment for pituitary deficiencies other than GH, and discontinuation of previous GH therapy for at least 1 year	QoL scales used: HSCL Shortened Dutch version of POMS STAI

Results
- No quantitative data presented
- No significant difference in psychological well-being

Comments

Methodological comments
- Randomisation method: Not given
- Similar baseline characteristics: IGF levels similar. No significant differences noted
- Patients blinded to treatment: Yes, but no details given
- Outcome assessors blinded to treatment: Yes, with details given
- Compliance: 2 patients had poor compliance
- Drop-outs and withdrawals: 2 patients were withdrawn due to poor compliance; 1 patient had incomplete data
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Yes
- One-way analysis of co-variance

General comments
- Conflict of interests: Funding support not mentioned
- Other: No data

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	1

MPHD, multiple pituitary hormone deficiencies

Adverse events

Withdrawals from trial

GH group (*n* = 32 with data analysed)		Placebo group (*n* = 12 with data analysed)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Total			

Note: Total n = *50; 2 patients withdrew due to difficulties with compliance, 2 others withdrew (but the reasons and from which group are uncertain), and data for analysis were not available for 1 patient*

***Adverse events* contd**

Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia		
Fluid retention/oedema		
Total number of events		
Total number of patients with events		

Note: Report states, "14 dose reductions in GH due to side effects", but it is not stated what specific "side effects" were experienced

Reference and design	Intervention	Participants	Outcome measures
Florkowski *et al.*, 1998[14] (New Zealand) Type of trial: Crossover Length of follow-up: 3 months, crossover for 3 months Jadad score: 1/5	Name of GH: Genotropin Administration timing and place: Daily subcutaneous injection by patients Dose: Up to 0.25 U/kg/week in daily doses Did any patients receive GH before trial?: 2 patients Other hormone replacements: 18 patients were receiving other hormone replacement treatments	Total number of participants: 20 adults Isolated or multiple deficiencies: 18 patients with multiple deficiencies, 2 patients with idiopathic AO- or CO-GHD: 16 patients with AO-GHD, 4 patients with CO-GHD Severity of GHD: GH < 3 µg/l following clonidine (0.15 mg/m^2) Sex: 17 men and 3 women Age: Mean, 47 years; range. 20–69 years Inclusion criteria: None given	QoL scales used: DSQ SCL-90 SAS

Results (at 3 months)	**GH start**	**GH end**	**Placebo start**	**Placebo end**
SCL (mean ± SE)	5.8 ± 1.2	4.0 ± 0.7	3.7 ± 1.2	2.5 ± 0.8
SAS (mean ± SE)	2.05 ± 0.12	1.9 ± 0.13	1.86 ± 0.1	1.73 ± 0.08
DSQ (mean ± SE)	10.8 ± 2.43	8.1 ± 2.4	8.6 ± 1.7	5.0 ± 2.1

- Small decrease (improvement), but this was found for both the GH and placebo arms

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: Crossover
- Patients blinded to treatment: Placebo supplied in identical vials
- Outcome assessors blinded to treatment: No information, assumed
- Compliance: No information
- Were all patients accounted for at trial conclusion?: Not given
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Except for other replacement therapies
- Two-way analysis of variance

General comments

- Conflict of interests: Funding support from Pharmacia & Upjohn

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	

Adverse events

- Crossover trial – did not describe adverse event data separately for GH versus placebo group
- No data reported on number of specific adverse events

Reference and design	Intervention	Participants	Outcome measures
Giusti *et al.*, 1998[15] (Italy) Type of trial: Parallel Length of follow-up: 6 months Jadad score: 2/5	Name of GH: Genotropin Administration timing and place: Subcutaneous injection daily before bedtime Dose: Starting dose of 0.5 U. Average daily dose of 3.7 µg/kg body weight. After adjustment, drug dose ranged from 0.5 to 1 U. Very low dose Did any patients receive GH before trial?: Unknown Other hormone replacements: Conventional substitution when indicated. All patients received other hormone replacement treatments, except 2 patients in the placebo group	Total number of participants: 26 (14 received GH and 12 received placebo) Isolated or multiple deficiencies: 2 patients with isolated and 24 patients with multiple deficiencies (assumed on basis of replacement therapy) AO- or CO-GHD: All outpatients with AO-GHD Severity of GHD: Peak serum GH response < 3.5 µg/l during insulin-induced hypoglycaemia Sex: 14 women and 12 men Age: Mean 51 years; range, 21–74 years Inclusion criteria: None of the patients suffered from serious psychiatric disease. All patients had a history of structural lesion of the pituitary	QoL scales used (at a psychiatric examination): Italian version of self-rating KSQ HDS

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
KSQ (mean ± SE)	23.8 ± 3.5	19.0 ± 4.0	24.4 ± 3.3	19.6 ± 3.5
HDS (mean ± SE)	27.9 ± 1.1	24.6 ± 0.8	28.6 ± 1.4	27.1 ± 1.1
KSQ subscales (mean ± SE):				
Anxiety	6.9 ± 1.2	5.6 ± 1.0	5.1 ± 0.8	4.5 ± 0.9
Depression	6.0 ± 1.3	4.0 ± 1.2	6.3 ± 1.0	4.5 ± 1.3
Somatisation	6.6 ± 1.2	5.4 ± 1.3	9.9 ± 1.9	9.3 ± 2.3
Hostility	4.9 ± 0.9	4.4 ± 1.2	2.3 ± 0.6	2.4 ± 0.6

• HDS: Significant reduction in depression in GH group ($p < 0.02$)

Comments

Methodological comments

• Randomisation method: Not given
• Similar baseline characteristics: Sex, age distributions and other variables were similar. No difference in KSQ scores at baseline. No difference in HDS scores
• Patients blinded to treatment: No details
• Outcome assessors blinded to treatment: No details
• Compliance: No information
• Drop-outs and withdrawals: 1 patient withdrew due to adverse events with GH (headache and swelling)
• Intention-to-treat analysis: No
• Aside from GH treatment, were the groups treated equally?: Yes
• Non-parametric tests

General comments

• Conflict of interests: Funding support not mentioned
• Other: Unsure about blinding

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial

GH group (*n* = 13)		Placebo group (*n* = 12)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Headache/swelling	1		
Total	1		0

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia		
Fluid retention/oedema	0	
Total number of events		
Total number of patients with events		

*Note: Paper states that, at 1 month, GH doses were reduced (*n *= 1) or increased (*n *= 5) according to three factors: IGF-I levels, resistance data evaluated by bioimpedance analysis and adverse effects. No details of individual adverse effects were given. At 3 months, GH dose was increased in 3 other patients and decreased in 1 due to "severe swelling"*

Reference and design	Intervention	Participants	Outcome measures
McGauley, 1989[16] (UK) Type of trial: Parallel, double-blind Length of follow-up: 6 months Jadad score: 2/5	Name of GH: Genotropin Administration timing and place: Self-administered subcutaneous injection at 10 pm Dose: 0.07 IU/kg body weight Did any patients receive GH before trial?: Not given Other hormone replacements: Pituitary replacement therapy	Total number of participants: 24 adults Isolated or multiple deficiencies: Multiple AO- or CO-GHD: Majority of patients acquired GHD in adulthood Severity of GHD: Defined as a GH concentration of < 3 mU/l during ITT Sex: Not stated Age: Range, 18–55 years	QoL scales used: NHP (part 1) PGWB

Results
- No quantitative results
- NHP: GH-treated patients significantly improved in relation to baseline (no differences in scores at entry)
- PGWB: No significant difference in scores

Comments

Methodological comments
- Randomisation method: Not given
- Similar baseline characteristics: Not given
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: Not given
- Were all patients accounted for at trial conclusion?: Not given
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Yes
- Unpaired *t*-test at entry and after 6 months (not appropriate)

General comments
- Conflict of interests: Funding support not mentioned

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	

Adverse events
Withdrawals from trial*

GH group (*n* = ?)		Placebo group (*n* = ?)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Total			

* n = *24 overall (numbers not clear in text)*

***Adverse events* contd**
Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia	5	
Fluid retention/oedema	6	
Total number of events	Unable to calculate	
Total number of patients with events		

Reference and design	Intervention	Participants	Outcome measures
McKenna *et al*., 1997[18] (abstract) (The Netherlands) Type of trial: Parallel RCT for 6 months, then open trial for 6 months Length of follow-up: 6 months (RCT) Jadad score: 1/5	Name of GH: Genotropin Administration timing and place: Subcutaneously each day Dose: 0.10 IU/kg/week for first 4 weeks, then increased to 0.20 IU/kg/week for 6 months. Maximum dose, 3 IU Did any patients receive GH before trial?: Not stated. Other hormone replacements: Not stated	Total number of participants: 30 patients Isolated or multiple deficiencies: Not stated AO- or CO-GHD: Not stated Severity of GHD: Not stated Sex: 15 men and 15 women Age: mean, 49 years Inclusion criteria: Not stated	QoL scales used: QoL-AGHDA NHP at 3 and 6 months

Results
- No quantitative results
- No results given for RCT, only those for open trial

Comments

Methodological comments
- Randomisation method: Not stated
- Similar baseline characteristics: No baseline characteristics reported
- Patients blinded to treatment: Not reported
- Outcome assessors blinded to treatment: Not reported
- Compliance: Not discussed
- Drop-outs and withdrawals: No reports of losses to follow-up
- Intention-to-treat analysis: Not reported
- Aside from GH treatment, were the groups treated equally?: Not reported

General comments
- Conflict of interests: Not stated, but one co-author employed by Pharmacia & Upjohn

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0

Adverse events
- No data provided

Reference and design	Intervention	Participants	Outcome measures
McKenna *et al.*, 1997[17] (abstract) (Spain) Type of trial: Parallel RCT for 6 months, open trial for 6 months Length of follow-up: 6 months Jadad score: 1/5	Name of GH: Genotropin Administration timing and place: Subcutaneously each day Dose: 0.125 IU/kg/week for first 4 weeks, then increased to 0.250 IU/kg/week for 6 months Did any patients receive GH before trial?: Not stated Other hormone replacements: Not stated	Total number of participants: 69 patients Isolated or multiple deficiencies: Not stated AO- or CO-GHD: Not stated Severity of GHD: Not stated Sex: 42 men and 27 women Age: mean, 37.7 years Inclusion criteria: Not stated	QoL scales used: QoL-AGHDA NHP

Results
- No quantitative results
- No results given for RCT, only those for open trial

Comments

Methodological comments
- Randomisation method: Not stated
- Similar baseline characteristics: No baseline characteristics reported
- Patients blinded to treatment: Not reported
- Outcome assessors blinded to treatment: Not reported
- Compliance: Not discussed
- Drop-outs and withdrawals: No reports of losses to follow-up
- Intention-to-treat analysis: Not reported
- Aside from GH treatment, were the groups treated equally?: Not reported

General comments
- Conflict of interests: Not stated but one co-author employed by Pharmacia & Upjohn

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0

Adverse events
- No data provided

Reference and design	Intervention	Participants	Outcome measures
de Novaes Soares *et al.*, 1999[19] (Brazil) Type of trial: Parallel RCT Length of follow-up: 6 months Jadad score: 3/5	Name of GH: Genotropin – Kabipen Administration timing and place: Self-administered subcutaneously Dose: 0.125 IU/kg/week for first month, then increased to 0.25 IU/kg/week for following 5 months Did any patients receive GH before trial?: All free of GH treatment for last 12 months Other hormone replacements: Not stated	Total number of participants: 10 patients (1 patient withdrew) Isolated or multiple deficiencies: 8 patients with multiple deficiencies and 1 patient with isolated deficiency AO- or CO-GHD: 7 patients with AO-GHD, 2 patients with CO-GHD Severity of GHD: Diagnosis by ITT, but figures not provided Sex: 6 men and 3 women Age: Mean, 39.4 years; range, 28–52 years Inclusion criteria: GHD for at least 2 years; no severe acute illness in last 6 months, chronic diseases or history of malignancy	QoL scales used: SADS HDS BDI Measurements of attention Cognitive tests

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
HDS (mean ± SD)	7.6 ± 5.81	2.2 ± 1.64	4.75 ± 1.26	2.5 ± 2.64
BDI (mean ± SD)	12.6 ± 7.02	4.2 ± 1.92	7.0 ± 3.16	4.5 ± 1.29

- HDS: Significant reduction in GH group ($p < 0.043$)
- BDI: Significant reduction in GH group ($p < 0.043$)

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: Very small number of patients – not discussed
- Patients blinded to treatment: Stated that double-blind but no information
- Outcome assessors blinded to treatment: Stated that double-blind but no information
- Compliance: No information
- Drop-outs and withdrawals: 1 patient withdrew
- Intention-to-treat analysis: No; 1 patient withdrew (not in results)
- Aside from GH treatment, were the groups treated equally?: Yes

General comments

- Conflict of interests: Funding support not mentioned

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

Adverse events

Withdrawals from trial*

GH group ($n = 5$)		Placebo group ($n = 4$)	
Reason	**Number**	**Reason**	**Number**
Oedema		Oedema	
Arthralgia		Arthralgia	
Total			

* *1 patient withdrawn before randomisation due to compliance issue*

***Adverse events* contd**

Number of specific adverse effects (excluding withdrawals)†

Type of adverse effects	GH	Placebo
Arthralgia		
Fluid retention/oedema		
Total number of events		
Total number of patients with events		

† *No data presented*

Reference and design	Intervention	Participants	Outcome measures
Verhelst *et al.*, 1997[20] (Belgium) Type of trial: Parallel Length of follow-up: 6 months Jadad score: 3/5	Name of GH: Genotropin Administration timing and place: Daily subcutaneous injections Dose: 0.125 IU/kg body weight/week for the first month, followed by 0.25 IU/kg body weight/week for the next 5 months, with a maximum dose of 4 IU/day. Dose adjustments made in case of adverse events or when deemed appropriate by the investigators Did any patients receive GH before trial?: 8 patients in the GH group and 5 patients in the placebo group, but not in the previous 12 months Other hormone replacements: Not stated, but assumed that 132 patients had MPHD (inclusion criteria specified stable hormone replacement therapy for at least 6 months)	Total number of participants: 148 patients (71 patients received GH and 77 patients received placebo) Isolated or multiple deficiencies: 16 patients had isolated GHD, 132 patients had multiple pituitary hormone deficiencies AO- or CO-GHD: 134 patients with AO-GHD, 14 patients with CO-GHD Severity of GHD: Peak serum GH < 10 mU/l in response to provocation testing by insulin-induced hypoglycaemia (89 patients), glucagon (35 patients) or clonidine (24 patients) Sex: 89 men and 59 women Age: mean of GH group, 43.5 years; mean of placebo group, 44.1 years Inclusion criteria: GHD present for at least 24 months. Aged between 20 and 60 years. Those with MPHD had been stable on hormone replacement therapy for at least 6 months	QoL scales used: NHP Social self-reporting questionnaire

Results

- No baseline measures provided
- Results depicted graphically relative to baseline of zero
- NHP scores improved greatly in patients on GH for all dimensions except social isolation, physical mobility and pain, but similar results were also obtained in the placebo group
- Compared with placebo, patients in the GH group tended to perform slightly better for emotions, energy and sleep, although the differences did not reach significance
- In contrast to the placebo group, patients in the GH group had no improvement in pain (p = 0.02); 16.7% of patients already had zero scores at baseline and could therefore not improve with therapy
- Note: One outcome of many considered

Comments

Methodological comments

- Randomisation method: Not stated
- Similar baseline characteristics: Similar age, sex ratio, age of diagnosis, aetiology and numbers of patients who previously had GH treatment
- Patients blinded to treatment: Paper states 'double-blind'. No further details
- Outcome assessors blinded to treatment: Paper states 'double-blind'. No further details, but dose adjustments could be made due to adverse effects
- Compliance: Not stated
- Drop-outs and withdrawals: 15 patients withdrew during the 6-month trial
- Intention-to-treat analysis: Not stated. Assuming not intention to treat
- Aside from GH treatment, were the groups treated equally?: Assumed
- p-values reported for change in QoL between start of study and end-point for both groups separately

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

continued

Adverse events
Withdrawals from trial*

GH group (*n* = 71)		Placebo group (*n* = 77)	
Reason	**Number**	**Reason**	**Number**
Oedema	0	Oedema	0
Arthralgia	0	Arthralgia	0
Total	0		0

* *15 patients withdrew after 6 months for other reasons*

***Adverse events* contd**
Number of specific adverse effects (reported as percentages)†

Type of adverse effects	GH	Placebo
Arthralgia	11	2
Peripheral oedema	9	1
Generalised oedema	4	0
Myalgia	3	0
Paraesthesia	2	0
Stiffness in extremities	2	1
Carpal tunnel syndrome	2	0
Depression	2	1
Dyspepsia	2	0
Nervousness	2	1
Hyperuricaemia	1	1
Flu	1	1
Hypertension	1	1
Headaches	1	1
Tendinitis	1	1
Tiredness	0	1
Insomnia	0	2
Cutaneous rash	0	2
Total number of events	44	16
Total number of patients with events	Unable to calculate	Unable to calculate

† *Presumed to be percentage of individual groups, although there appears to be some misreporting. Numbers were calculated from percentages reported*

Reference and design	Intervention	Participants	Outcome measures
Wallymahmed *et al.*, 1997[21] (UK) Type of trial: Double-blind, placebo-controlled, parallel design for first 6 months, then open for the second 6 months Length of follow-up: 6 months for RCT, then open for 6 months Jadad score: 3/5	Name of GH: Genotropin Administration timing and place: daily subcutaneous injections (7 per week) given at bedtime Dose: 0.125U/kg/week for first month, then 0.25 U/kg/week for 5 months. GH dose was reduced if side-effects occurred Did any patients receive GH before trial?: 2 patients received GH in childhood Other hormone replacements: Corticosteroids: 14 patients in GH group vs 5 patients in placebo group ($p < 0.05$) Thyroxine: 11 patients in GH group vs 5 patients in placebo group Sex steroids: 13 patients in GH group vs 7 patients in placebo group DDAVP: 5 patients in GH group vs 3 patients in placebo group	Total number of participants: 35 patients enrolled, 30 completed the study. Patient descriptions are on the 30 who completed the study Isolated or multiple deficiencies: Eligibility criteria specified patients with hypothalamic pituitary disorders and GHD attending the neuroendocrine clinic at Walton Hospital, Liverpool; 15 patients had pituitary adenomas, 8 craniopharyngiomas, 7 intracranial tumours AO- or CO-GHD: All except 2 patients had AO-GHD Severity of GHD: Peak serum GH level (mU/l) in GH group (mean ± SD), 2.5 ± 2.5; in placebo group, 3.8 ± 3.2 Sex: GH group, 7 men and 10 women; placebo group, 3 men and 10 women Age (mean ± SD): GH group, 37 years ± 12.9; placebo group, 33 years ± 11.2. Age range not provided Inclusion criteria: None given	QoL scales used: LFS Impact Scale NHP HADS SES MFS

Results (at 6 months)	GH start	GH end	Placebo start	Placebo end
NHP (mean ± SE):				
Energy	1.76 ± 1.0	1.05 ± 0.9	1.30 ± 1.1	0.84 ± 1.2
Emotional reactions	2.52 ± 2.9	1.82 ± 2.7	1.38 ± 1.5	1.53 ± 2.1
Social isolation	0.52 ± 0.9	0.76 ± 1.2	0.62 ± 1.0	0.92 ± 1.4
Sleep	1.35 ± 1.4	1.41 ± 1.4	1.15 ± 1.3	1.00 ± 1.4
Pain	1.29 ± 2.1	2.0 ± 2.8	0.84 ± 1.3	1.15 ± 1.9
Physical mobility	0.88 ± 1.1	1.58 ± 1.8	0.61 ± 1.0	0.92 ± 1.2
Impact Scale (mean ± SE)	22.1 ± 8.2	19.1 ± 7.5	22.1 ± 5.7	21.1 ± 7.3
LFS (personal)	34.0 ± 13.0	38.1 ± 16.6	29.6 ± 9.5	39.5 ± 13.4
LFS (material)	11.1 ± 7.4	17.2 ± 14.6	9.6 ± 5.3	15.8 ± 12.7
SES	27.8 ± 4.9	28.5 ± 5.9	28.4 ± 3.5	30.9 ± 4.4
MFS	20.5 ± 8.9	18.2 ± 8.1	15.8 ± 4.3	15.5 ± 6.0
Anxiety	7.8 ± 3.4	7.3 ± 3.4	6.6 ± 2.9	5.5 ± 3.3
Depression	5.5 ± 2.8	5.1 ± 3.2	4.6 ± 3.0	4.7 ± 4.5

Within-group comparisons

- NHP: Significantly reduced energy score in GH group ($p < 0.01$). No differences for other subsections
- HADS: No significant changes
- SES: Self-esteem increased significantly in placebo group but not in GH group
- MFS: No significant changes in mental fatigue questionnaire
- Impact Scale: Significant reduction in the perceived impact of GHD in the GH group
- LFS: Significant increase in personal fulfilment in placebo group. Significant increase in material fulfilment in GH group
- Did not analyse overall results from QoL scales

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: No, more men in GH group, peak serum GH level lower in GH group, significantly more patients receiving corticosteroids in GH group, and more patients receiving thyroxine, sex steroids and DDAVP in GH group
- Patients blinded to treatment: Yes, but no details given
- Outcome assessors blinded to treatment: Yes, but no details given. However, side-effects could have alerted assessors to grouping
- Compliance: Assessed at visits every 3 months, by self-reported number of injections missed and by inspecting the returned GH vials (used and unused). No information given on results of this assessment
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: No, different requirements for other hormones
- Used a paired *t*-test to assess within-group differences, between the end-point and the baseline for each group (not appropriate)

continued

***Comments* contd**

General comments

- Conflict of interests: Funding support not mentioned
- Other: QoL was assessed for up to 3 years of GH replacement
- Baseline characteristics only given on the 30 patients who completed the 12-month study
- Results taken at 6 months (end of RCT); authors of this review have not included results at 12 months (after a further 6 months, but open design)
- GH dose was reduced if side-effects occurred – query possible impact on blinding
- Two patients in the GH group withdrew when dose reduction did not reduce side-effects of treatment
- Incorrect statistical analysis, plus subgroup analysis
- No information on compliance assessment
- Query minimum age

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

DDAVP, 1-deamino-8-D-arginine vasopressin

Adverse events

Withdrawals from trial

GH group (*n* = 19)		Placebo group (*n* = 13)	
Reason	**Number**	**Reason**	**Number**
Oedema and/or arthralgia	2	Oedema	
Total	2		

***Adverse events* contd**

Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Fluid retention/oedema and/or arthralgia	8	1*
Mild transient side-effects	4	3
Total number of events		
Total number of patients with events	12	4

* *Paper reports that, in the first few months, there were 11 patients reporting side-effects that warranted dose reductions; all but 1 of these patients were on active treatment when the symptoms presented (8 in GH–GH group and 3 in placebo–GH group). Therefore, 2 patients in the placebo group must have had the symptoms once in the open trial*

Reference and design	Intervention	Participants	Outcome measures
Whitehead *et al.*, 1992[22] (UK) Type of trial: Crossover Length of follow-up: 6 months of treatment, 1 month of washout, 6 months of treatment Jadad score: 2/5	Name of GH: Genotropin Administration timing and place: 7 nightly subcutaneous injections Dose: 0.5 U/kg/week Did any patients receive GH before trial?: Not stated Other hormone replacements: 11 patients received substitution therapies	Total number of participants: 14 Isolated or multiple deficiencies: 11 patients had multiple deficiencies, 3 patients had isolated deficiency AO- or CO-GHD: 6 patients with AO-GHD, 8 patients with CO-GHD Severity of GHD: Peak GH < 7 mU/l in response to insulin-stimulated hypoglycaemia Sex: 5 women and 9 men Age: Mean, 29.4 years; range, 19.5–52 years	QoL scales used: NHP PGWB Schedule

Results

- No quantitative results given
- NHP could not be assessed because several values were equal pre- and post-treatment
- Psychological well-being was unaltered by GH treatment
- No significant difference in trabecular spinal bone mineral content (after GH treatment, 130.7 mg/cm^3; after placebo, 133.7 mg/cm^3)

Comments

Methodological comments

- Randomisation method: Not given
- Similar baseline characteristics: Not necessary (crossover)
- Patients blinded to treatment: Yes
- Outcome assessors blinded to treatment: Yes
- Compliance: Patients asked to record daily injections on a log sheet and return empty vials. Compliance was very good, from 87% to 100%, except for withdrawals
- Drop-outs and withdrawals: 4 withdrawals
- Intention-to-treat analysis: No
- Aside from GH treatment, were the groups treated equally?: Not necessary
- *t*-test for a crossover design. All data were tested for treatment as well as carry-over effects. If there was a carry-over effect, the *t*-test was modified accordingly

General comments

- Conflict of interests: Funding support from KabiVitrum Ltd, Sweden
- Other: No figures (only after GH and placebo)

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	1

Adverse events

Withdrawals from trial

GH group*		Placebo group*	
Reason	**Number**	**Reason**	**Number**
Oedema	1	Oedema	0
Arthralgia	0	Arthralgia	0
Carpal tunnel syndrome	1	Carpal tunnel syndrome	0
Inconvenience of injection	0	Inconvenience of injection	1
Amblyopia	0	Amblyopia	1
Total	2		2

* *Total* n = *14 (no* n *given for study arms because crossover trial)*

***Adverse events* contd**

Number of specific adverse effects (excluding withdrawals)

Type of adverse effects	GH	Placebo
Arthralgia		
Fluid retention/oedema	1	
Pain in knees and shoulders	1	
Back pain	1	1
Total number of events	3	
Total number of patients with events	2	1

Appendix 7

Adverse events data

Study	Rates of oedema		Difference (rate in GH group minus placebo group)
	Placebo group	GH group	
Attanasio *et al.*, 1997[6] (AO-GHD)	4.3%	28.8%	Increase of 24.5%
Attanasio *et al.*, 1997[6] (CO-GHD)	0	6.3%	Increase of 6.3%
Baum *et al.*, 1998[7]	0	10%	Increase of 10%
Bengtsson *et al.*, 1993[8] *			
Beshyah *et al.*, 1995[9]	20%	35%	Increase of 15%
Burman *et al.*, 1995[10] *			
Cuneo *et al.*, 1998[11]	30%	48%	Increase of 18%
Degerblad *et al.*, 1990[12] *			
Deijen *et al.*, 1996[13]	No data presented		
Florkowski *et al.*, 1998[14] *			
Giusti *et al.*, 1998[15]	0	0	
McGauley, 1989[16]	No data presented		
McKenna *et al.*, 1997[17]	No data presented		
McKenna *et al.*, 1997[18]	No data presented		
de Novaes Soares *et al.*, 1999[19]	No data presented		
Verhelst *et al.*, 1997[20]	1.2%	18%	Increase of 16.8%
Wallymahmed *et al.*, 1997[21]	No data presented		
Whitehead *et al.*, 1992[22] *			

* *Crossover trial – data combined for both placebo and GH groups*

Study	Rates of arthralgia		Difference (rate in GH group minus placebo group)
	Placebo group	GH group	
Attanasio *et al.,* 1997[6] (AO-GHD)	6.5%	23.1%	Increase of 16.6%
Attanasio *et al.*, 1997[6] (CO-GHD)	0	6.3%	Increase of 6.3%
Baum *et al.*, 1998[7]	0	0	—
Bengtsson *et al.*, 1993[8] *			
Beshyah *et al.*, 1995[9]	0	10%	Increase of 10%
Burman *et al.*, 1995[10] *			
Cuneo *et al.,* 1998[11]	13%	30%	Increase of 17%
Degerblad *et al.*, 1990[12] *			
Deijen *et al.,* 1996[13]	No data presented		
Florkowski *et al.*, 1998[14] *			
Giusti *et al.*, 1998[15]	0	0	
McGauley, 1989[16]	No data presented		
McKenna *et al.*, 1997[17]	No data presented		
McKenna *et al.*, 1997[18]	No data presented		
de Novaes Soares *et al.*, 1999[19]	No data presented		
Verhelst *et al.*, 1997[20]	15.5%	2.5%	Increase of 13%
Wallymahmed *et al.*, 1997[21]	No data presented		
Whitehead *et al.*, 1992[22] *			

* *Crossover trial – data combined for both placebo and GH groups*

Appendix 8

Safety reporting in GH replacement therapy

A systematic search for information on the safety of GH in adults was outside the remit of this report. However, because adverse events might not occur in the context of relatively small trials, some additional safety data were sought. One study reported on serious adverse events that were in the Pharmacia database as of mid-1995.[78] Adverse events reported in the context of included trials have already been mentioned. In addition, some professional associations have considered the evidence about safety, and there are few relatively small trials focused specifically on safety.

The Pharmacia database study[78] reviewed the data from 2978 adults with GHD. The majority of patients had been in treatment for 12 months (1983 patients). Others had received treatment for 18–24 months (491) or 36 months (64). Therefore, data from truly long-term treatment were not available. Six patients died. The causes were variable, and there was no obvious connection with GH treatment.

In this database, there were 9 cases of diabetes mellitus. Six of these patients showed signs of the disease prior to starting GH treatment, therefore it was concluded that GH is not a potent inducer of diabetes mellitus in non-predisposed adults. The prevalence of diabetes mellitus is increased in adults with hypopituitarism, and one of the actions of GH is insulin antagonism. Therefore, assessment of glucose metabolism is recommended before and during GH treatment.[2,24,79] In diabetic adults, such monitoring should be intensified along with eye examination. The development of preproliferative changes and the presence of proliferative retinopathy are contraindications to GH replacement.[24,79] There have also been instances of pancreatitis associated with GH therapy.[24]

In the database study,[78] there were seven patients with myocardial infarction aged between 42 and 61 years. Another five patients aged between 42 and 62 years reported angina pectoris for the first time. There were single cases of atrial fibrillation, pericarditis and bradycardia. Epilepsy was reported in 15 patients, all of whom had convulsions previously. There was no information about the adequacy of or compliance with anticonvulsive therapy.

There has been concern about the possibility that GH may be implicated in an increased risk of malignancy. The consensus statement of the Growth Hormone Society[79] reports no data to support the theory that IGF-I and IGF-binding protein-3 might modulate cancer risk in patients treated with GH, although it is recommended that levels of IGF-I be maintained within age- and gender-related normal ranges over long-term therapy. Although an increased incidence of certain malignancies has been reported in adults with hypopituitarism, there is no evidence of a relationship with GH replacement.[79] The database study[78] reported new benign or malignant tumours in 11 patients, but there was no pattern in pathology, age of patients or duration of GH therapy. A total of 44 'pituitary adverse events' were reported. Among these, no evidence for pituitary tumour recurrence could be found in ten patients. Pituitary tumours recurred in 20 patients, and pituitary tumours were identified in 14 patients. It was concluded that information available in the database about tumour recurrence is currently insufficient to determine whether GH influences the risk of tumour recurrence.

Additional problems associated with GH replacement include fluid retention, especially early in treatment. Fluid retention in conjunction with oedema of the extremities, carpal tunnel syndrome, arthralgia and myalgia were more frequently encountered in early clinical trials in which doses were higher than currently recommended.[24] These problems generally resolved within 1–2 months while therapy was continued.

GH treatment may unmask incipient hypothyroidism, and therefore thyroid function should be monitored along with glucocorticoid status.[79] GH replacement increases serum levels of lipoprotein(a); however, the clinical implications of this are uncertain.[79]

Transient gynaecomastia has been reported in adults receiving GH treatment.[24]

Supraphysiological doses of GH in intensive care settings have been shown in two RCTs to double the mortality rate.[79] However, there are no data to support the discontinuation of GH replacement in patients who become critically ill or who are receiving intensive care treatment.

One study considered adults with CO-GHD and AO-GHD.[80] Within each of these groups, participants were randomised to GH treatment or placebo in a double-blind design. This phase was followed by an open-label treatment phase. During the double-blind therapy phase, only two adverse events occurred more frequently in the GH-treated patients (oedema and peripheral oedema), and these events occurred only in the patients with AO-GHD. Other reported adverse events included arthralgia, myalgia, headache, joint disorder and paraesthesia. This study was not of sufficient size to detect small differences in the occurrence of relatively rare adverse events. However, it was found that adverse events were more common in patients with AO-GHD than in those with CO-GHD. Among the patients with AO-GHD, there was greater risk of adverse events among those who were heavier. It should also be noted that this study used GH doses based upon body weight, rather than the now standard set daily dose. Therefore, these adverse events may be less likely with the smaller doses now routinely administered.

Appendix 9

Studies using the QoL-AGHDA

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
Badia *et al.*, 1998[36] (Spain) 1-year longitudinal, observational QoL study	No	356 consecutive adult GH-deficient patients with peak GH ≤ 10 mU/l after a stimulation test, diagnosed after the age of 18 years, from the endocrinology units of 37 hospitals were included over a 6-month period The patients had to have concomitant pituitary hormone deficits and pituitary hormone replacement therapy for at least 6 months prior to the study Those previously treated with GH or with a previous history of acromegaly were excluded from the study	• Mean QoL-AGHDA score for patients at baseline was 9.4 (95% CI, 8.4 to 10.4) and at 12 months 10 (95% CI, 8.8 to 11) • Scores were worse in older patients with a low level of education, lower income levels, and associated chronic disease and poor self-reported health status • Mean QoL-AGHDA score in controls (standardised for age and education) was 5.49 (95% CI, 5.27 to 5.71)	• Placebo effect not excluded • Non-randomised design • 36 drop-outs from the study • 287 patients answered QoL-AGHDA at 12 months • Clinically selected study group Authors' conclusion: The results permit comparison of patients' scores against reference scores with regard to the desirable effect of treatment
Abs *et al.*, 1999[37] KIMS (Pharmacia & Upjohn International Metabolic Database)	No intervention	1034 adult patients with hypopituitarism (53.5% men) and GHD (peak GH response < 10 mU/l), 275 of whom (27%; 136 men, 139 women) were not previously treated with GH (naive patients) Patients in MONICA trial (geographical variation in the major risk factors of coronary heart disease in men and women aged 35–64 years) were used as the comparator group of normal adults	QoL-AGHDA scores: **Mean (95% CI)** • Naive patients: – Overall 7.1 – Men 6.1 (6.0 to 8.2) – Women 10.2 (9.1 to 11.3) – CO-GHD 9.6 (6.7 to 12.7) – AO-GHD 8.7 (7.8 to 9.5) • Normal adults in MONICA trial: – Men (2.7 to 3.3) – Women (4.0 to 4.6)	• Possibly biased control group Authors' conclusion: The elevated QoL-AGHDA scores indicate that QoL was markedly impaired in GH-deficient patients in KIMS

continued

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
Wiren *et al.*, 2000[27] (Sweden)	No intervention	111 patients with GHD (72 men, 39 women) were recruited from outpatient endocrinology clinic (peak GH < 9 mU/l in response to ITT) Stable replacement of all other pituitary hormone deficiencies was established Random sample from adult population, all from outpatient clinic (63% agreed to participate) Normative scores based on 1448 people	• QoL-AGHDA unidimensional • QoL-AGHDA similar hierarchical order for different populations (ordinal scale, little differential item functioning) • Justification to report mean ± SD for Rasch-transformed QoL-AGHDA scores • Raw score: median (interquartile range) – Controls 2.0 (0.0–5.0) – Patients 9.0 (2.0–13.0) • Rasch-transformed QoL-AGHDA scores (0–100) – Controls 20.3 ± 18.2 – Patients 38.4 ± 21.4	Author's conclusion: The Swedish QoL-AGHDA is suitable for assessing QoL in adults with GHD
Barkan, 2001[38] (USA)	No intervention	20 patients with severe adult-onset hypopituitarism (9 women, 11 men; mean age, 49.4 years). The known duration of hypopituitarism was at least 4 years. Other hypopituitary hormone deficits were replaced 22 patients with acromegaly (7 women, 15 men; mean age, 46.7 years). The duration of active acromegaly was 4–45 years; 10 patients were newly diagnosed, and 12 were previously treated with transsphenoidal surgery Staff and faculty of the Divisions of Endocrinology and Neurosurgery served as a control group	QoL-AGHDA scores: **Mean ± SD** • Normal controls 3.3 ± 0.7 • Patients with hypopituitarism 10.6 ± 1.5 ($p < 0.001$, compared with control group) • Patients with active acromegaly 11.6 ± 1.6 ($p < 0.001$, compared with control group)	Authors' conclusion: The QoL-AGHDA was unable to discriminate between patients with hypopituitarism and patients with acromegaly. Because the QoL-AGHDA cannot distinguish between the extremes of GH output, its ability to detect an improvement in QoL during GH replacement has to be viewed with scepticism

continued

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
McKenna *et al.*, 1999[25] (UK, Sweden, Germany, Italy and Spain)	GH replacement in part of the groups in Sweden, Germany and Italy The dose and duration of GH treatment were not stated	GH-deficient adults from the UK (55 adults, 17.6% with CO-GHD, 46% men), Sweden (82 adults, 23.3% with CO-GHD, 55% men, 41 GH treated), Germany (34 adults, 69% with CO-GHD, 82% men, 6 GH treated), Italy (44 adults, 29.5% with CO-GHD, 66% men, 34 GH treated) and Spain (38 adults, 66% men)	QoL-AGHDA scores: **Median** **Mean ± SD** • UK – Treated patients – Untreated patients 10.0 8.7 ± 7.2 • Sweden – Treated patients 2.0 3.1 ± 4.3 – Untreated patients 8.0 8.1 ± 6.4 • Germany – Treated patients 2.0 3.0 ± 4.1 – Untreated patients 4.0 5.7 ± 5.8 • Italy – Treated patients 6.0 6.6 ± 5.5 – Untreated patients 8.0 9.2 ± 7.2 • Spain – Treated patients – Untreated patients 5.0 5.7 ± 5.1 • Coefficients of reliability in different countries, 0.86–0.95 • Good correlations with PGWB and NHP subscales of energy level, emotional reactions and physical mobility	• Non-randomised design • No comparative group of no intervention (placebo effect not excluded) Authors' conclusion: Each language version of QoL-AGHDA is shown to have good reliability, internal consistency and construct validity
Monson *et al.*, 2000[81] KIMS	GH replacement initiated at a maximum dose of 0.042 mg/kg/week, with a subsequent increment to a maximum of 0.083 mg/kg/week based on individual requirement and responsiveness	109 patients (66 men) aged > 65 years, commencing GH replacement 863 patients aged < 65 years and with AO-GHD, who have not received GH for at least 6 months prior to entry into KIMS, 220 of whom went on to complete > 6 months GH therapy in KIMS	QoL-AGHDA scores (read from graph): • Patients aged < 65 years – Men Baseline (mean ± SD) 8.5 ± 6.2 Mean change at 6 months –1.9 ($p < 0.001$) – Women Baseline (mean ± SD) 10.6 ± 6.9 Mean change at 6 months –3.8 ($p < 0.001$) • Patients aged > 65 years – Men Baseline (mean ± SD) 7.0 ± 6.4 Mean change at 6 months –2.6 ($p < 0.05$) – Women Baseline (mean ± SD) 9.2 ± 6.4 Mean change at 6 months –1.7 (not significant)	• Non-randomised design • No comparative group of no intervention (placebo effect not excluded) Authors' conclusion: The data confirm similar baseline characteristics and positive benefit from GH replacement in older compared with younger patients with hypopituitarism, particularly in relation to QoL

continued

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
Drake *et al.*, 1998[40] (UK)	48 patients started at a dose of 0.8 IU/day, and 2 patients (with essential hypertension or impaired glucose tolerance) at 0.4 IU/day Median dose in men (0.8 IU/day; range, 0.4–1.6 IU/day) was significantly lower than that of women (1.2 IU/day; range, 0.8–2.0 IU/day; $p < 0.0001$) Median time to reach a maintenance dose of GH was significantly shorter in men (4 weeks; range, 2–12 weeks) than in women (11 weeks; range, 2–26 weeks; $p < 0.0001$)	50 consecutive patients with adult-onset hypopituitarism (17 men and 33 women; mean age, 45 years) with peak GH ≤ 9 mU/l in response to a stimulation test; treatment managed by a dose-titration regimen (start dose, 0.8 or 0.4 IU/day) 21 patients with GHD previously treated using a weight-based regimen (6 men, 15 women; mean age, 34 years)	QoL-AGHDA scores (mean ± SD): • Pretreatment, 14.2 ± 5.9 • At 3 months of GH replacement, 7.4 ± 4.5 ($p < 0.001$) • At 6 months of GH replacement, 7 ± 5.5 • No gender differences • AGHDA scores at 6 and 12 months of GH replacement were not statistically different from 3 and 6 months, respectively • Maintenance AGHDA scores in the 21 patients treated with a weight-based regimen were not statistically different from patients whose GH dose was titrated *de novo*	• No control group Authors' conclusion: QoL improvement was observed in 94% of patients. The improvement was sustained at 6 and 12 months. In terms of QoL improvement, the efficacy is not compromised by the use of a dose-titration regimen
Murray *et al.*, 1999[41,42] (UK)	GH replacement was commenced at 0.8 IU/day and subsequently adjusted by increments of 0.4 IU/day at intervals of at least 4 weeks	65 severely GH-deficient patients with peak GH < 9 mU/l in response to provocation testing (40 women, 25 men; mean age, 38.7 years; age range, 17–72 years), with replacement of other pituitary hormones and who presented with subjectively poor QoL at the endocrine outpatient department	QoL-AGHDA scores: **Mean ± SD (*n*)** • Overall – Baseline 15.3 ± 6.0 (63) – At 3 months 10.4 ± 6.2* (49) – At 6 months 9.8 ± 6.5* (39) – Overall change –5.5 • Men – Baseline 13.9 ± 6.3 (24) – At 3 months 9.0 ± 6.0† (20) – At 6 months 6.5 ± 4.7* (13) – Overall change –7.4 • Women – Baseline 16.1 ± 5.8 (39) – At 3 months 11.4 ± 6.3* (29) – At 6 months 11.4 ± 6.7* (26) – Overall change –4.7 • Patients with AO-GHD – Baseline 16.0 ± 5.7 (45) – At 3 months 11.2 ± 6.4* (31) – At 6 months 11.6 ± 6.2* (26) – Overall change –4.4 • Patients with CO-GHD – Baseline 13.3 ± 6.4 (18) – At 3 months 9.1 ± 5.8† (18) – At 6 months 6.2 ± 5.7* (13) – Overall change –7.1 • In untreated GH-deficient adults, the degree of perceived QoL impairment was influenced by the age at which GHD developed • Patients with AO-GHD expressed a greater level of distress • The degree of QoL improvement with GH replacement depended on the baseline QoL score and the age of onset of GHD • The degree of QoL improvement was independent of gender, pathology and number of pituitary hormone deficits * $p < 0.01$; † $p < 0.05$	• Drop-outs not analysed • No control group Authors' conclusion: Patients with CO-GHD in whom QoL is significantly reduced show a capacity to benefit that is equal to, if not greater than, that seen in patients with AO-GHD

continued

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
Davies *et al.*, 2000[43] (UK)	GH at an initial dose of 0.01 IU/kg/day, increased after 1 month to 0.015 IU/kg/day for men and 0.02 IU/kg/day for women	All patients with hypopituitarism and diagnosed GHD (GH < 10 mU/l in response to standard provocation testing) 39 adults (20 men, 19 women; mean age, 46.4 years; peak GH, 1.4 ± 2.1 mU/l) agreed to participate; 24 patients (10 men, 14 women; mean age, 54.2 years; peak GH, 2.9 ± 2.7 mU/l) declined GH treatment	QoL-AGHDA scores: **Mean ± SD** – Baseline 10.0 ± 4.0 – At 3 months 7.0 ± 4.1 ($p < 0.001$) • Significant correlation between the percentage change in body composition and change in QoL score ($r = 0.34$, $p < 0.05$)	• Study design is a before-and-after study without a control group Authors' conclusion: GH therapy may make a major difference to the quality of a patient's life, and despite the cost, withholding treatment in the face of convincing evidence is difficult to justify
Bulow & Erfurth, 1999[44] (Sweden)	GH (Genotropin) was given with a commencing dose of 0.5 IU/day. The dose was increased over 2 weeks to 1.5 IU/day and adjusted according to the response to IGF-I. The median GH dose at the end of the study was 1.5 IU/day (range, 1.0–2.0)	10 patients (8 men, 2 women) with CO-GHD (peak GH ≤ 1.6 mU/l in response to insulin-induced hypoglycaemia), 3 of whom had isolated GHD and 7 multiple pituitary deficiencies When required, replacement of other pituitary deficiencies was provided for at least 6 months before inclusion in the study	QoL-AGHDA scores: **Median (range)** – Before GH replacement 6 (1–23) – After 9 months of GH 2 (0–18) • Significant QoL improvement after 9 months of GH treatment ($p = 0.008$)	• Not randomised • Not placebo controlled Authors' conclusion: All patients but one reported improvement in QoL. Because the present study was not randomised or placebo controlled, placebo effects cannot be ruled out as an explanation for the present findings
McKenna *et al.*, 1997[18] (The Netherlands)	For the first 4 weeks of each 6-month period, the GH dose was 0.10 IU/kg/week, followed by 0.20 IU/kg/week Daily subcutaneous injections	30 patients (15 men, 15 women; mean age, 49 years) were randomly assigned to receive placebo or GH for 6 months, and then all patients were treated with GH for 6 more months	• There was a statistically significant improvement ($p < 0.01$) in QoL-AGHDA scores from baseline to the end of the trial, when all patients were receiving GH	• Results were not reported for the GH treatment and placebo groups • Placebo effect could not be excluded • No comparison group results were presented Authors' conclusion: The results of the Dutch trial show that the QoL-AGHDA is a unidimensional scale. It was shown to be responsive within the context of a clinical trial, because QoL improved with GH replacement therapy

continued

Reference and design	GH treatment	Participants	QoL-AGHDA outcome measures and results	Comments and study authors' conclusion
McKenna *et al.*, 1997[17] (Spain)	For the first 4 weeks of each 6-month period, the GH dose was 0.125 IU/kg/week, followed by 0.250 IU/kg/week Daily subcutaneous injections	69 patients (42 men and 27 women; mean age, 37.7 years) were randomly assigned to receive placebo (19 men and 16 women) or GH (23 men and 11 women) for 6 months, and then all patients were treated with GH for 6 more months	• There was a statistically significant improvement (11.1 vs 6.9, $p < 0.0001$) in QoL-AGHDA scores from baseline to the end of the trial, when all patients were receiving GH	• Results were not reported for the GH treatment and placebo groups • Placebo effect could not be excluded • No comparison group results were presented Authors' conclusion: The results of the trial show that the Spanish version of the QoL-AGHDA is a uni-dimensional instrument, providing valid and reliable scores for QoL. The QoL-AGHDA was able to detect clear improvements in QoL with GH replacement therapy

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ISSN 1366-5278