Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation

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Authors' objectives
To examine the clinical effectiveness of growth hormone (GH) therapy in adults with either adult-onset or childhood-onset growth hormone deficiency (GHD), using impact on quality of life (QoL) as the outcome measure.

Searching
The following electronic databases were searched up to May 2001: MEDLINE (from 1985), EMBASE (from 1989), the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register (Issue 4, 2001), HealthSTAR (from 1975), NHS EED, PubMed, the Science Citation Index and Social Sciences Citation Index, BIOSIS Previews, EconLit, PsycINFO, Index to Scientific and Technical Proceedings, HMIC, NLM Gateway and the National Research Register. The search terms were given. In addition, the journal Clinical Endocrinology was handsearched from August 1993 to August 2000. The references of retrieved articles were also checked and relevant researchers were contacted. Industry submissions to the National Institute of Clinical Excellence were searched and a list of trials was requested from industry. Only studies in English were included in the review.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) and systematic reviews of RCTs were included in the review.

Specific interventions included in the review
Studies comparing any dose of biosynthetic human GH (somatropin) were eligible for inclusion in the review. The typical doses of GH in the included studies ranged from 0.25 to 0.5 IU/kg per week. The duration of treatment in the vast majority of the studies was 6 months (range: 3 to 21).

Participants included in the review
Adults diagnosed with GHD, including those who were continuing GH treatment from childhood, were eligible. Participants with both adult-onset and childhood-onset GHD were included in the review. The mean age of the patients was approximately 40 years (range, where reported: 17 to 74). In most trials there was a preponderance of males.

Outcomes assessed in the review
Studies that reported outcomes of QoL measures were eligible. Twenty-three different QoL measures were included in the review. The four most commonly used were the General Health Questionnaire (GHQ), Hamilton Depression Scale (HDS), Psychological General Well-Being (PGWB), and Nottingham Health Profile (NHP) and its subscales.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened both titles and abstracts for inclusion in the review. Any disagreements were resolved through discussion.

Assessment of study quality
The validity of the trials was assessed using the Jadad scale. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion.
Methods of synthesis

How were the studies combined?
The studies were combined in meta-analyses where appropriate numerical data were available and where the QoL measures were homogeneous. Fixed-effect and random-effects models were employed depending on the degree of heterogeneity. A narrative synthesis was employed for the remainder of the evidence from included studies, which were summarised in evidence tables.

How were differences between studies investigated?
Differences between the studies on the QoL scales used were explored in the narrative synthesis and by applying meta-analyses to appropriate subgroups. Where a meta-analysis was employed, a chi-squared test for heterogeneity was carried out.

Results of the review

Seventeen RCTs with 892 patients were included in the review. The sample size ranged from 6 to 173.

Ten trials used the NHP to evaluate health-related QoL. The four trials that reported effect sizes for the 6 dimensions of the NHP were pooled for each subscale. The pooled estimates showed non significant differences between placebo and GH for: the energy subscale (score increase: 0.29, 95% confidence interval, CI: -0.86, 1.43, P=0.63); the pain subscale (score increase: 3.04, 95% CI: -1.96, 8.04, P=0.23); the emotional reactions subscale (points change: 2.41, 95% CI: -2.78, 7.61, P=0.36); the sleep subscale (points change: 0.14; 95% CI: -0.05, 0.33, P=0.15); and the physical mobility subscale (points change: 0.52, 95% CI: -0.42, 1.45, P=0.28). There was a significant degree of statistical heterogeneity between the trials on all these scales, with the exception of sleep. The pooled estimates showed a significant result favouring GH over placebo for the social isolation scale (points change: -0.26, 95% CI: -0.39, -0.12, P=0.0002).

Three trials used the GHQ to evaluate health-related QoL, and two of these reported the GHQ scores for the patient groups. These trials were pooled to give a summary estimate of changes in QoL of 5.08 points; this favoured placebo but was non significant (95% CI: -2.76, 12.96, P=0.20).

Two trials used the HDS to measure depression. The pooled estimate of these trials showed a non significant benefit of GH therapy (points change: -2.43, 95% CI: -4.94, 0.07, P=0.06).

Four trials used the PGWB to evaluate health-related QoL, and two of these reported the GHQ scores for the patient groups. These trials were pooled to give a summary estimate of changes in QoL of 2.14 points; this favoured GH but was non significant (95% CI: -4.10, 8.38, P=0.50).

The rates of oedema and arthralgia were found to be higher in patients receiving GH than in the placebo group. The rates of oedema were reported to be between 10 and 24.5% higher in the GH group, whilst the rates of arthralgia were between 6 and 17% higher.

Cost information

Yes. There were no appropriate, published cost-effectiveness or cost-utility studies or models available. Three cost studies were identified. Drug cost is the single most important factor in determining treatment costs. There was a small difference in the relative cost of adult-onset GHD, compared with childhood-onset GHD, due to differences in the overall length of GH therapy. There is a need for better evidence on the impact of GH replacement on the length and QoL of GHD patients before a cost per quality-adjusted life-year can be estimated for each condition.

Authors’ conclusions

The trials have not demonstrated any consistent QoL benefit of GH therapy in adults with GDH.

CRD commentary

This was a well-conducted review with clear inclusion criteria. The search was reasonably comprehensive, although the
restriction to studies in English may have led to the introduction of language bias. Appropriate measures were used to minimise bias and error in the study selection and data extraction processes. The primary studies were presented in detail in summary tables. The use of meta-analyses was restricted to studies from which it was clinically meaningful to pool the data; the narrative synthesis used for the rest of the studies and outcomes was appropriate. The authors' conclusions were appropriately cautious given the quality and heterogeneity of the evidence included in the review.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to develop methods for the interpretation of changes in QoL scores. These methods should then be applied in well-designed trials which could, for example, determine the optimal dosing strategy.

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