The Effectiveness and Cost-effectiveness of Somatostatin Analogues in the Treatment of Acromegaly

Report commissioned by: West Midlands Development and Evaluation Service

Produced by: The Aggressive Research Intelligence Facility (ARIF) & The West Midlands Development and Evaluation Service, Department of Public Health, University of Birmingham, UK.

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Recommendation: Borderline, but that somatostatin analogues be made available as a treatment option

Date completed: **June 2001 (Economic Evaluation updated February 2002)**

Expiry Date:

There are no known ongoing randomised controlled trials on the use of somatostatin analogues in the treatment of acromegaly.

If more reliable estimate of the level of benefits becomes available, the review of effectiveness and economic evaluation will have to be adjusted accordingly.

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West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

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CONTRIBUTIONS OF AUTHORS

David Moore was lead reviewer and chief author. DM & Lesley Roberts undertook independent data extraction and quality assessment. Catherine Meads and Fujian Song advised on the economic evaluation. Fujian Song was also the main editor.

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LIST OF ABBREVIATIONS USED IN THE TEXT AND TABLES

ARIF	Aggressive Research Intelligence Facility
BNF	British National Formulary
BP	Blood pressure
C	Comparator
CNS	Central Nervous System
DARE	Database of Abstracts of Reviews of Evidence
DES	Development and Evaluation Service
F	Female
GH	Growth Hormone
GHRA	Growth Hormone Receptor Antagonist
GHRH	Growth Hormone Releasing Hormone
I	Intervention
IGF-1	Insulin-like Growth Factor-1
Im	Intramuscular
ITT	Intension to treat analysis
L	litre
M	Male
Mg	milligrammes.
MI	Myocardial infarction
Ml	millilitre
N	Number
N/A	Not available
N/M	Not measured
Nmol	nanomoles
N/S	Not significant
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
OGTT	Oral Glucose Tolerance Test
P	Probability
QALY	Quality-adjusted life-year
Sc	Subcutaneous
SEM	Standard error of the mean
U	Units
µg	microgrammes.

1 SUMMARY

1.1 Background

Acromegaly is a relatively uncommon disorder of disproportionate growth due to long-term exposure to elevated levels of growth hormone. The primary cause of the disease is a pituitary tumour. Clinical features of the disease include soft tissue proliferation, skeletal alterations, cardiovascular problems and hormonal imbalance. The annual incidence of the disease is approximately 4 cases per million people with a prevalence of about 20-40 cases per million. Mean age of onset is estimated to be 30-40 years. Mortality rates are 1-3 times that of an age and sex matched population, with life expectancy reduced by about 10 years.

1.2 Current Practice

Management of acromegaly is complex with multifarious treatment options. The aim of treatment is to reduce circulating growth hormone levels to normal. Surgery to remove or debulk the pituitary tumour is the primary treatment. Radiotherapy is used for those patients for whom surgery is not an option or where a tumour has not been totally removed by surgery. The intention of both of these procedures is to be curative. Where radiotherapy is contra-indicated or while it takes effect medical adjuvant treatment is usually given. Traditionally dopamine agonists have been used for medical treatment but more recently somatostatin analogues have been developed. Somatostatin analogues have also been suggested as a primary treatment and as neo-adjuvant treatment prior to surgery. Currently two somatostatin analogues (octreotide and lanreotide), in the form of three preparations (octreotide sc, octreotide LAR, lanreotide LA), are available.

1.3 Objectives and Methods

This systematic review aims to examine the clinical effectiveness and costs of somatostatin analogue treatment for acromegaly.

Four questions were addressed in this review. These were:

(a) What is the effectiveness of somatostatin analogues versus conventional therapy as an adjuvant treatment to surgery and or radiotherapy?
(b) What is the effectiveness of somatostatin analogues compared to conventional therapy as a primary treatment for acromegaly?
(c) What is the effectiveness of somatostatin analogues as a neo-adjuvant treatment to surgical removal of a pituitary tumour in acromegaly?
(d) What is the effectiveness of the different somatostatin analogues in the treatment of acromegaly?

The Cochrane Library, MEDLINE, EMBASE, PubMED, CINAHL, Science Citation Index, NHS EED, abstracts of presentations at major endocrinological conferences, relevant pharmaceutical companies were searched or contacted for evidence of clinical effectiveness and to inform the economic evaluation.

1.4 Result on Effectiveness

The results were:

(a) Three RCTS have been undertaken on the effectiveness of somatostatin analogues as adjuvant treatment to pituitary surgery and or radiotherapy in acromegaly. Two of the RCTs compared octreotide sc to placebo and one RCT compared octreotide sc to the dopamine agonist bromocriptine. All three trials were of relatively short duration, two enrolled relatively small numbers of patients and the quality of all three was mediocre. From these trials octreotide sc appears more effective than placebo and equally as effective as bromocriptine. Robust research with longer follow up is required to clarify whether octreotide sc is more effective than bromocriptine. In addition further research is required to address the fact that no controlled trials have compared the effectiveness of octreotide LAR or lanreotide LA with dopamine agonists and cabergoline in particular. Furthermore no controlled trial has investigated the effectiveness of combined somatostatin analogue and dopamine agonist treatment compared to single drug treatment.

(b) No studies met the inclusion criteria with regard to the effectiveness of somatostatin analogues as a primary treatment for acromegaly. Trials may be deemed unethical with regard to most patients, as the aim of the main comparators (surgery, radiotherapy) is a cure rather than the control of symptoms.

(c) Two RCTs have been undertaken on the effectiveness of somatostatin analogues as neo-adjuvant treatment to surgical resection of a pituitary tumour causing acromegaly. One trial employed octreotide sc and the other lanreotide LA. In general, the quality and reporting of both trials was poor and therefore it is not possible to determine the effectiveness of somatostatin analogues as neo-adjuvant treatment.

(d) Only one RCT has compared the effectiveness of different somatostatin analogues. The trial compared octreotide LAR treatment with lanreotide LA over a three month period. Although the trial determined that octreotide LAR was more effective than lanreotide LA, weaknesses in the study design and reporting mean that the findings of this RCT cannot be relied upon to give dependable information on the effectiveness of one analogue over the other. The effectiveness of octreotide sc compared to depot somatostatin analogue preparations (octreotide LAR, lanreotide LA) has not been assessed by RCT. No reliable evidence exists from RCTs on which to make a recommendation of one somatostatin analogue over another.

1.5 Economic Evaluation

No published cost utility analysis on somatostatin analogues in the treatment of acromegaly were identified. An apparent cost effectiveness analysis was identified through searching conference abstracts although the only fully published article arising from this abstract essentially reports a cost study.

The economic evaluation in this review concentrated on adjuvant medical treatment. An analysis of costs per year of treatment with somatostatin analogues (octreotide LAR and lanreotide LA) compared to dopamine agonists (bromocriptine and cabergoline) was undertaken, as was modelling to estimate incremental costs per life year saved and incremental costs per QALY of the interventions.

The estimated cost for the first year of treatment with somatostatin analogues is £11,544 (estimated range £9,329-£13,728) for octreotide LAR and £9,328 (estimated range £9,046-£15,874) for lanreotide LA. Estimated costs for dopamine agonists are approximately 10 times cheaper at £824 (estimated range £514-£1,110) for bromocriptine and £996 (£649-£2,101) for cabergoline. It is evident from these values that within class costs are similar. The estimated costs for the second year of treatment are similar to those of the first year for each treatment.

Decision analytic modelling reveals that the incremental cost per life year saved for somatostatin analogue over cabergoline is £64.5M (range 29M-300M) and the incremental cost per QALY is £530K (range 253K-3.2M). These estimates are based on data from observational studies, or subjective assumptions.

1.6 Future Research

More robust and longer term research on all the situations in which somatostatin analogues can be employed in the treatment of acromegaly is required in order to provide data from which the effectiveness and cost effectiveness of treatment can be ascertained.

2 AIM OF THE REVIEW

This review arose from a request to ARIF for information on the effectiveness of somatostatin analogues in the treatment of acromegaly from a consultant in public health medicine within the West Midlands NHS region. The consultant's interest stemmed from a request by a local endocrinologist for funding for the use of somatostatin analogues. Searches by Aggressive Research Intelligence Facility (ARIF) found no systematic reviews but did indicate that a number of trials had been undertaken on the subject. The request was passed to the West Midlands Development and Evaluation Service (DES) as a potential topic for a systematic review.

The broad aim of this review was to determine the effectiveness and cost effectiveness of the use of somatostatin analogues verses conventional therapies in the treatment of acromegaly.

3 BACKGROUND

Acromegaly is a relatively uncommon, insidious, debilitating disorder of disproportionate growth. The disease develops over many years due to long term exposure to elevated levels of growth hormone (GH) caused in most cases by a pituitary tumour. The term acromegaly is Greek in origin, derived from *akron* meaning extremity and *megale* meaning great. This description typifies some of the characteristic clinical features of the disease which include disproportionate enlargement of the hands, feet and facial features. Retrospectively the disease has been ascribed as the cause of the clinical features detailed in the 14 century BC Egyptian king Akhenaton, and in Goliath, the biblical giant defeated by David.[1] It has also been suggested as the inspiration for the Mr Punch puppet caricature.

The clinical features of acromegaly are associated with the effects of GH hypersecretion and compression of the tissues surrounding an expanding tumour.[2] Progressive cosmetic disfigurement and systemic organ manifestations are the classic features. Patients may exhibit any number of the following clinical features:

Soft Tissue Proliferation:	hands, feet, facial features, tongue, nose, lips, skin tags
Skin Alterations:	thickening, increased sweating & oiliness, acne
Skeletal Alterations:	bone overgrowth, premature osteoarthritis, carpal tunnel syndrome
Cardiovascular Problems:	cardiac muscle weakness, enlarged heart, hypertension
Endocrine Problems:	hormonal imbalance, diabetes mellitus, cessation of menstruation, impotence
Neurological Problems:	tingling in extremities, visual field defects
Respiratory Problems:	breathing difficulty, breathing cessation during sleep
Malignancy:	colon polyps
Other:	headache, fatigue

Due to the progressive nature of the disease early diagnosis may be missed until the symptoms are pronounced to a level where they already have a marked effect on the patients lifestyle.

3.1 Growth Hormone

Before discussing the causes of acromegaly it is perhaps pertinent to review briefly the physiology and measurement of growth hormone secretion.

GH is the primary influence on growth after birth and is secreted by the pituitary (Appendix I). This secretion is influenced by the action of growth hormone releasing hormone (GHRH) which stimulates GH release, and somatostatin, which inhibits it. The systemic growth effects of GH are mainly mediated through the action of circulating insulin-like growth factor (IGF-1) which is produced by the liver under the direct positive influence of GH (Appendix I).[3] Pituitary GH secretion is under circadian influence and modulated by a number of factors such as ingestion of glucose which suppresses secretion. These factors, combined with a short biological half life of ≈22 minutes, give rise to a pulsatile pattern of secretion that results in 6-11 circulating GH peak/trough cycles of differing amplitude and duration per day.[3]

Measurement of circulating GH has to account of this variation in GH secretion. Serum GH concentration is reported as either the mean of several measurements taken at intervals over many hours or measured after suppression of secretion by a fasting glucose ingestion, known as an oral glucose tolerance test (OGTT). An oral glucose tolerance test is regarded as being the most reliable.[4] In contrast to GH, circulating IGF-1 (see Appendix I) has a longer biological half-life of 2-4 hours due to the protective effects of associated specific carrier proteins. Therefore it has a more stable circulating level and can be assessed by a single measurement. Other factors can be measured to assess change in symptoms. For example finger ring size measurement can be used as a marker for the degree of soft tissue swelling.

3.2 Causes of Acromegaly

Approximately 99% of all cases of acromegaly are caused by GH hypersecreting pituitary adenomas, and approximately 12% of all pituitary tumours cause acromegaly.[5] Rarely (1%), acromegaly results from ectopic (non-pituitary) tumours, which secrete either GH or growth hormone releasing hormone.[6,7] Given the rarity of acromegaly and the very low prevalence of these ectopic tumours, they are not specifically considered in this report. Hypersecretion of GH not only elevates circulating GH but consequentially IGF-1, resulting in disproportionate growth and the multitude of clinical features previously described. Some GH secreting pituitary adenomas (25%) may also hypersecrete prolactin resulting in the impotence, lactation and cessation of menstruation seen in acromegaly.[2]

3.3 Diagnosis

Diagnosis of acromegaly is often delayed for a number of reasons. Patients and their families may not be aware of the slowly progressiving changes to facial features and extremities. Given that the symptoms of acromegaly are various and cover a range of medical disciplines, a patient who presents to their GP with one predominant symptom will most likely be treated or referred to a specialist for that condition only. As such it may be several years later, on the development of subsequent symptoms, that acromegaly is suspected and the patient is referred to an endocrinologist. Once acromegaly is suspected, definitive diagnosis involves determination of elevated circulating GH (by an oral glucose tolerance test) and IGF-1, and tumour visualisation/localisation by computer tomography or magnetic resonance imaging. The delay from the onset of the disease until diagnosis

has been estimated at 5-10 years, but this period is expected to decrease due to advances in information/education, diagnostic assays and the radiological detection of tumours.[2]

3.4 Epidemiology

The annual incidence of acromegaly in the European population is approximately 4 cases per million people, with a prevalence of about 40-60 per million. No gender, racial or socio-economical predispositions have been identified.[8,9] Therefore, an average UK health authority, with a population of half a million people, will have 20-30 cases. Only about 10% of GPs are likely to currently care for a patient with acromegaly and only 30% of GPs will encounter a new case in their career.
The mean age at diagnosis is 42 years old. The delays in diagnosis suggest the mean age of onset is between 30-40 years. Mortality rates in patients with acromegaly are 1-3 times higher than that of an age and sex matched population, and life expectancy is reduced by 10 years, due to increased rates of cardiovascular, cerebrovascular, respiratory and malignant disease.[2] The presence of diabetes or hypertension may further increase the mortality rate.[10]

3.5 Current Service Provision

The most important factors in the treatment of acromegaly are to remove any immediate tumour effects such as visual field defects due to a tumour pressing on the optic chiasm, and to reduce circulating levels of GH. Reduction and ultimately normalisation of circulating levels of GH is strongly associated with a reduction in symptoms and improved mortality.[11] The threshold below which a serum GH level is classed as nominally safe or normalised has progressively been reduced.[12,13] Recent proposals suggests treatment should aim to reduce serum GH to < 2.5µg/l (5mU/l) as measured by mean serum levels, or <1µg/l (2mU/l) if measured by oral glucose tolerance test. Studies have shown that below these levels the life expectancy of patients with acromegaly is equivalent to the general population.[11,14] However <5µg/l (mean) and <2µg/l (OGTT) are still used.[15-17] It is important to note that many patients experience some degree of symptomatic relief with only a modest reduction in circulating GH (and IGF-1) but with levels much higher than these thresholds.

The treatment options in acromegaly are complex, multifarious and dependent on, amongst other parameters, the size and location of the tumour, co-morbidity, patient age and patient preference (Daggett P, Stafford General Hospital, Stafford, UK; Stewart P, Department of Medicine, University of Birmingham, UK: personal communications, 2000).[17] Established interventions are surgery, radiotherapy, dopamine agonists and somatostatin analogues with the aim of the first two being curative and the last two methods of controlling symptoms.

3.5.1 Surgery

Surgical extraction or debulking of the tumour to reduce GH secretion, and or compression is currently the preferred primary treatment for most patients. Contraindications are co-morbidity, patient age (usually >70 years when surgical trauma carries a greater risk than the remainder of life with active acromegaly), likelihood of a poor outcome, and patient preference. Two surgical methods are employed, transsphenoidal and transcranial adenomectomy. Transsphenoidal surgery is

the least invasive and most common procedure. Conversely transcranial surgery, being more traumatic for the patient, is normally only indicated in rare invasive tumours. Surgical outcome is dependant on the experience of the surgeon, the preoperative GH level and the size and extension of the tumour. Microadenomas (diameter < 1cm) have better outcome than macroadenomas (diameter > 1cm).[18] Estimates suggest that even with an experienced surgeon, 20% of patients with microadenomas and 50% of patients with macroadenomas do not achieve 'safe' levels of GH & IGF-1 post surgery.[17] These patients require additional treatment with either radiotherapy directed at the tumour or medical therapy using dopamine agonists or somatostatin analogues, to further reduce hormone levels (see below). A small minority of patients undergo a second round of surgery. Side effects of surgery include leakage of cerebrospinal fluid, meningitis and hypopituitarism.

3.5.2 Radiotherapy

Radiotherapy has traditionally been the choice of therapy where surgery is not indicated or has not been totally successful.[17] The goal of radiotherapy is to reduce GH & IGF-1 by maximising dose to the tumour whilst minimising surrounding tissue damage.[19] Various therapeutic techniques have been employed.[20] Application of radiation usually occurs in 20-30 fractions spread over 4-5 weeks until a maximal dose to the tumour is achieved. The benefits of such radiotherapy are dose dependent and delayed, with GH levels progressively declining to normal levels in most patients 10-20 years after therapy.[17,20] Medical adjuvant therapy (dopamine agonists or somatostatin analogues) is often given during this lag period to provide interim symptomatic relief. A number of side effects are associated with radiotherapy including hypopituitarism, visual dysfunction, secondary brain malignancy, brain necrosis and other brain dysfunction.[17] Hypopituitarism is the most common and increases in incidence the longer the post treatment period.[20]

3.5.3 Dopamine Agonists

In healthy individuals dopamine agonists bring about release of GH, however, paradoxically dopamine agonists suppress GH hyper-secretion in some acromegaly patients. The precise mechanism of both these actions is still unclear although it is believed that dopamine agonists act directly on dopamine receptors on the tumour cells, with differential responses between patients due to receptor density.[17,21] Several dopamine agonists have been used to treat acromegaly, including bromocriptine and cabergoline, and are administered orally on a daily (bromocriptine) or weekly (cabergoline) basis.[17,22] Historically, dopamine agonists, and bromocriptine in particular, facilitated the relief of symptoms in patients with acromegaly prior to the availability of other pharmaceutical treatments. Not all patients respond to treatment and in those that do, the majority do not reach normal GH levels. Dopamine agonists also reduce prolactin levels in patients with concomitant hyper-secretion of prolactin.[23] Side effects associated with dopamine agonists include nausea, vomiting, postural hypotension, constipation, arrhythmia and CNS effects. The profile of side effects varies between agonists and therefore patients intolerant of one may be given another. Similarly patients may be more responsive to one agonist than another. Recently combination therapy with dopamine agonists and somatostatin analogues has been proposed.[23]

3.5.4 Growth Hormone Receptor Antagonists

Growth Hormone Receptor Antagonists are a new and as yet unlicensed treatment for acromegaly. Growth hormone receptor antagonists do not inhibit secretion of GH but block the action of circulating GH by binding to cell surface GH receptors with greater affinity but without eliciting a biochemical response. A randomised double blind placebo controlled trial of a genetically engineered growth hormone receptor antagonist has recently been completed and published.[24] Given that growth hormone receptor antagonists are still in development, with long term efficacy and safety still to be established to an extent to facilitate licensing, these drugs will not be considered in this review.

3.6 Intervention Under Review- Somatostatin Analogues

Being an inhibitor of GH secretion somatostatin generated interest as a natural therapeutic intervention for acromegaly. However, it possesses a biological half-life in the human circulation of approximately three minutes, which is too short to be of practical benefit.[25] Modification to prevent enzymatic degradation has lead to the development of somatostatin analogues. Two analogues, octreotide (Sandostatin®, SMS 201-995) (Novartis Pharmaceuticals UK Ltd) and lanreotide (Somatuline®, BIM23014) (Ipsen Ltd), are used for the relief of symptoms associated with acromegaly and other neuroendocrine tumours (Appendix II).[22] Octreotide is also licensed for the prevention of complications following pancreatic surgery. A third analogue, vapreotide (RC-160), is not as yet licensed or used for the treatment of acromegaly.

The specific indications for octreotide in patients with acromegaly is short term treatment prior to pituitary surgery, long term treatment in those not adequately controlled by other treatment or until radiotherapy becomes effective, and in patients for whom surgery is inappropriate. Lanreotide is indicated in acromegaly when circulating levels of GH remain abnormal after surgery and/or radiotherapy.[22]

Octreotide is available in two forms in the UK. A standard formulation for subcutaneous injection (octreotide sc, Sandostatin) at a dose of 100-200µg three times daily and as a micro-encapsulated long acting depot preparation, octreotide LAR (Sandostatin LAR), administered intra-muscularly (gluteal muscle) initially at 20mg every 28 days, in those patients adequately controlled by octreotide sc. Dose can be varied according to symptoms up to a maximum of 30mg every 28 days. Patients can be trained to self inject octreotide sc but octreotide LAR injections are administered by health care professionals. Studies have been undertaken on the continuous subcutaneous infusion of octreotide sc but this modality is not routinely available in the UK.

Lanreotide is available as lanreotide LA (lanreotide SR, lanreotide PR, Somatuline LA), a long acting depot preparation administered intra-muscularly in one injection of 30mg every 14 days by a health care professional. The frequency of injections can be increased depending on the patient's response, commonly to every 7-10 days.[22]

In addition to their use as an adjuvant therapy with or without dopamine agonists, somatostatin analogues have been recently proposed as primary treatment in place of surgery and radiotherapy and as a pre-surgical (neo-adjuvant) treatment to reduce tumour size and increase ease of resection.

Studies have demonstrated the existence of number of different types of cell surface somatostatin receptors and that the density of these receptors varies between tumours. The receptors possess differing affinities for octreotide and lanreotide.[26] Thus the efficacy of a particular analogue in a particular patient may be dependent on the type and density of the receptors within the tumour. Although not routinely undertaken, patients can be assessed to ascertain the likely response to treatment with somatostatin analogues using scintigraphy. In this procedure radiolabelled somatostatin analogue is injected in to the systemic circulation of the patient and computer tomograph or magnetic resonance imaging used to detect the degree to which it binds to the receptors in the tumour.

Somatostatin analogues are associated with a number of side effects, which include gallstone formation, abdominal pain, fat malabsorption, nausea, transient pain at injection site and bradycardia.[17] Treatment should be avoided in pregnancy and breast feeding as growth retardation has been demonstrated in animal studies.[22]

4 REVIEW METHODS

The methodology of this review was guided by the West Midlands Development and Evaluation Service handbook.[27]

4.1 Existing Reviews

No Cochrane review or other systematic reviews on somatostatin analogues in the treatment of acromegaly were identified, nor has a protocol for a Cochrane review been lodged on the Cochrane Library. Only general reviews have been published. The Midland Therapeutic Review and Advisory committee has compiled reports on both octreotide and lanreotide with respect to prescribing in a primary care environment.[28,29] The advice of both reports was that primary prescription should be restricted to those GPs with personal experience of the condition or where the GPs intend to gain specific experience and have close, appropriate and effective specialist support links.

Given the lack of a systematic distillation of the evidence of the effectiveness and cost effectiveness of somatostatin analogues in the treatment of acromegaly, this report aimed in part to fill this void.

4.2 Developing the Protocol

The protocol for this report was developed using literature identified through a scoping search of bibliographic databases concentrating on review articles.[27] In addition information was obtained from local clinical experts treating patients with acromegaly. All this information was used to inform the background to the review, to formulate the review questions and to refine the search strategies. The protocol was subjected to internal scrutiny and appropriate amendments were made.

4.3 Defining the Review Questions

Given the multifarious management options for acromegaly and the differing positions that somatostatin analogues can occupy within this management structure, dialogue was held with endocrinologists, treating large and small cohorts of patients, and a public health consultant to ascertain the most important factors with regard to the prescription of the analogues. From these discussions the following four questions were apparent.

Adjuvant Treatment

- What is the effectiveness of somatostatin analogues versus conventional therapy in the treatment for patients with acromegaly where the disease is not satisfactorily controlled by surgery and/or radiotherapy?

Primary Treatment

- What is the effectiveness of somatostatin analogues versus conventional therapy as a primary treatment for acromegaly?

Neo-Adjuvant Treatment

- What is the effectiveness of somatostatin analogues as pre-surgical treatment for acromegaly?

Analogue Comparison

- What is the effectiveness of one somatostatin analogue compared to another in the treatment of acromegaly?

Given that surgery is the treatment of choice, the first of these questions, the effectiveness of somatostatin analogues as an adjuvant therapy where surgery has not been totally successful or radiotherapy has yet to have its full effect, was considered by all those consulted to be the most important with regard to prescribing. Rather than solely address this question or to lump all four questions into one, it was decided that this review would address each question separately, so that the fundamentals of all the questions could be adequately addressed.

Preliminary searches indicated that there were likely to be a number of randomised and non-randomised controlled trials published on somatostatin analogues in the treatment of acromegaly. It was decided that for the question on adjuvant therapy included studies should be limited to studies with these designs. For the other three questions study design was limited to randomised controlled trials (RCTs) only.

For pragmatic reasons it was decided that the economic evaluation would only be undertaken for adjuvant therapy.

4.4 Search strategy

A broad and comprehensive search strategy was developed which was designed to identify any potentially relevant material on somatostatin analogue treatment for acromegaly. The main elements were:

- Electronic searches of MEDLINE and EMBASE using text and subject headings for acromegaly, somatostatin analogues, octreotide, lanreotide and alternative analogue names (Appendix III)
- Electronic searches of Cochrane Library controlled clinical trial register, CINAHL, PubMed, Science Citation Index
- Searches of endocrinology related conference presentations (The Endocrinology Society Annual Meeting 1999, 6th International Pituitary Conference 1999)
- Contact with experts and relevant pharmaceutical companies
- Citation checking of all included articles

As the first research on somatostatin analogues emerged in the 1970s and only records on MEDLINE precede this period, all electronic databases were searched without date restrictions. No language restrictions were applied.

Searches were conducted in April 2000.

The resulting pool of studies served two purposes. First, it could be scanned directly for studies relevant to the adjuvant treatment section of the review. Second, it was limited by the application of methodological filters (Appendix III) to identify RCTs to provide a list of trials from which studies

relevant to primary treatment, neo-adjuvant treatment and analogue comparison sections of the review could be identified.

The resulting sets of search results were then sifted using the following common methodology.

4.5 Inclusion and exclusion criteria

Initially one reviewer (DM) scanned titles and abstracts of all identified studies for relevance to the specific questions. The titles and in some instances the abstracts of foreign language papers were translated to facilitate this process. Irrelevant studies were eliminated from further scrutiny. Hard copies of all relevant publications were obtained along with copies of those where insufficient information was available to make a decision. These latter copies were scanned on receipt and those that were irrelevant were eliminated from further scrutiny.

Full translations of all foreign language papers reaching this stage were obtained.

Decision on the inclusion or exclusion of the studies reaching this final stage were undertaken using predetermined criteria by a single reviewer (DM). The included studies were RCTs (plus non-randomised controlled trials for adjuvant treatment) of patients with acromegaly treated with any somatostatin analogue compared to other appropriate treatment or placebo or no treatment. The precise inclusion and exclusion criteria for each of the questions address by the review are detailed in Appendix IV. For the adjuvant question, the criteria defining the population allowed the inclusion of trials where the majority rather than all of the patients had previously undergone surgery and /or radiotherapy. Ideally, these trials including patients who had not undergone surgery and/or radiotherapy should be excluded from this section of the review. However, no trial has included patients after surgical and/or radiotherapy only. Included studies were cross-checked for correct application of the criteria by a second reviewer (LR). Any discrepancies were resolved by discussion and if necessary with reference to a third reviewer. Each decision was made independently of detailed scrutiny of the results of the studies. Reviewers were not blinded against authors, their affiliations or journal in which the papers were published.

Duplicate publications from the same study would only be included if data on new outcome measures were reported. Where these publications also reported the same outcome measures only data on the original full population or subsets stratified at randomisation would be included.

The authors of one abstract of a conference presentation meeting the inclusion criteria, but for which a full publication was not available, were successfully contacted for further information.

A record was kept of all decisions and the number of studies eliminated at each stage.

Any studies that provided cost effectiveness or quality of life information were obtained to inform the economic evaluation.

4.6 Quality Assessment Strategy

The methodological quality of included studies was measured using the Jadad checklist[30] (Appendix V), which was applied independently by two reviewers (DM, LR) with discrepancies being resolved by discussion. Responses to the Jadad checklist can be given a cumulative score from 0 to 5, with a high score indicating higher methodological quality. Additional detail on methodological detail was recorded as part of the data extraction process. All data on quality were tabulated along with the Jadad quality score.

4.7 Data Extraction Strategy

Data was extracted from included studies independently by two reviewers (DM, LR) using a data extraction proforma (Appendix VI). The proforma was designed to be generic and therefore suitable for extracting data relevant to all four review questions. Discrepancies in extracting the data were resolved by discussion. Data were then tabulated for each review question into separate tables for study characteristics, quality and outcomes.

4.8 Economic Analysis

A review of the literature on the costs and health economic impact of somatostatin analogue treatment for acromegaly was undertaken. The original broad clinical effectiveness search was expanded to capture relevant economic analyses or articles reporting cost effectiveness data by running specific searches of MEDLINE, EMBASE, NHS EED, DARE, GEAR, Bandolier and Drug and Therapeutics Bulletin (Appendix III). Relevant information found during the clinical effectiveness searches was also used.

An economic analysis was only conducted with regard to medical interventions used as adjuvant to surgery and or radiotherapy. A simple decision tree was developed using information found during the undertaking of this review (Appendix X). All costs were estimated using whatever information could be obtained from published and unpublished sources. Information on mortality, quality of life and efficacy was obtained from relevant identified studies. The source of all information employed was documented, as were any assumptions. The costs, mortality and quality of life information were combined to obtain values for an incremental cost per life year saved and incremental cost per quality adjusted life year for somatostatin analogue versus treatment with dopamine agonists.

5 RESULTS

5.1 Somatostatin Analogues as Adjuvant Treatment

5.1.1 Quantity of Research Available

Initially 893 references were identified by the formal search and scrutinised (Appendix VII). 827 were immediately rejected on the basis of information in the title or abstract. 66 hard copies were obtained either because a decision could not be made due to insufficient information or because the studies were potentially relevant for inclusion. Part translations were obtained of 2 articles (Italian, Polish) to facilitate making a decision. 33 papers were immediately rejected as irrelevant based on information contained within the previously unseen abstracts and the remaining 33 papers were subjected to formal assessment against the inclusion and exclusion criteria. 6 papers comprising reports of 3 RCTs were included in the final analysis. The main reasons for exclusion were non-adherence to the criteria for study design and population, and outcomes measured after single dose(s) of somatostatin analogue. A list of included papers and papers excluded at this final stage, with reason for exclusion, are contained in Appendix VIII. There were no disagreements between reviewers when included studies were cross-checked for correct application of the inclusion criteria.

Of the three included trials two compared octreotide sc to placebo and one compared octreotide sc to dopamine agonist bromocriptine. Therefore no trials were found on octreotide LAR or lanreotide LA compared to any other medical treatment, placebo or no treatment. Trials were not found of octreotide sc compared to the dopamine agonist cabergoline nor were trials of any combination therapies for adjuvant treatment in acromegaly identified.

5.1.2 Characteristics and Quality of Included Studies

Detailed information on the characteristics and methodological quality of the included studies is tabulated in Appendix IX. The key features of these tables are described below.

The two placebo controlled trials, by Fredstorp and colleagues and Ezzat and colleagues, were double blinded and involved 20 and 116 patients respectively, 10 and 60 of whom received octreotide sc three time daily. The duration of treatment was short at 2 and 4 weeks respectively.[31-35] The bromocriptine controlled trial, by Halse and colleagues, was of open design and involved 26 patients, 13 of whom received octreotide. The duration of treatment was short at 8 weeks.[36]

In all three trials patient inclusion criteria were primarily based on a standard diagnosis for acromegaly of serum GH levels >2µg/l throughout an OGTT. The patient populations possessed a mean age in the range 45-55 years and did not appear to be atypical of patients with acromegaly. Previous treatments for acromegaly undergone by the patients were identified in each trial. The majority of patients in all three trials had undergone pituitary surgery. However, 20% of patients in the trial by Halse and colleagues and 35% in the trial by Fredstorp and colleagues had not undergone previous treatment with surgery, radiotherapy or bromocriptine. Similar precise figures were not available from the trial by Ezzat and colleagues. The presence of these untreated patients to some extent limits the applicability of the findings of these trials in determining the effectiveness of somatostatin analogues as an adjuvant treatment to surgery or radiotherapy. This is particularly

true for the trial by Fredstorp and colleagues where half of the placebo group were untreated. There were other within-study differences in the number of other previous treatments between the arms of these two trials.

All three trials incorporated a washout period of one month for patients taking dopamine agonists at enrolment. With regard to treatment, defined dose escalation of intervention and comparator was employed in all studies and dose frequency and dose sizes were within the recommended ranges.[22] The primary outcomes measured by all three trials were mean serum GH and IGF-1. Secondary outcomes measured by some but not all trials included other biochemical markers, signs and symptoms, tolerance and adverse events.

The quality of trials as assessed by a Jadad score was neither good nor bad at 2 or 3 out of 5. More specifically, the placebo controlled trials had poor description of randomisation. Concealment of allocation was unclear in all three trials. With regard to outcomes, only the trial by Halse and colleagues measured any patient centred outcomes and this was an assessment of symptoms using a disease specific questionnaire.

Statistical analysis of results was not complete in two of the trials. The trials by Ezzat and colleagues and Halse and colleagues only evaluated the change from baseline values for patients in the treatment group and placebo/comparator group separately. Statistical comparison was not undertaken between groups and insufficient information was given to enable this to be carried out independently. Further analysis would have been helpful in interpreting the results of the trial by Ezzat and colleagues as at baseline the mean GH level in the treatment group was double that of the control arm. Whether this difference is statistically significant is not reported in the publications of this trial, although when contacted a trialist reported that there was no significant difference between the two groups at baseline (Ezzat S, Mt. Sinai Hospital, Toronto, Canada: personal communication, 2000). The third trial, by Fredstorp and colleagues, evaluated the difference between groups at the same outcome assessment points but did not take into account the change from baseline to the assessment point.

Follow up rates for major outcomes were generally good, being greater than 80%, although in the study by Ezzat and colleagues it was difficult to identify from which arm and at what point some patients dropped out of the study or were lost to follow up.

The trial by Ezzat and colleagues followed the controlled phase of the trial with an open labelled dose comparison phase. Many of the outcomes measured for this trial were only reported as part of this dose comparison phase and not for the placebo controlled phase. The findings presented in this review are purely based on information from the placebo controlled phase of the trial.

5.1.3 Evidence about Effectiveness

Detailed information on the evidence of effectiveness from the included studies is tabulated in Appendix IX. The key features of the table are described below.

5.1.3.1 Placebo Controlled Trials

In the two placebo controlled trials beneficial effects of octreotide sc treatment over placebo on both mean GH and IGF-1 levels were reported (Figure 1).

In the trial by Ezzat and colleagues there was a significant reduction from baseline in mean GH and IGF-1 levels in the intervention group (change in mean levels: -74% and -50% respectively), whilst there were minimal changes in the placebo group (change in mean levels: +5% and -10% respectively) (Figure 1). In the trial by Fredstorp and colleagues mean GH levels in the octreotide sc group were reduced by treatment and were significantly lower than those of the placebo group at all time points after baseline measurements (change in mean GH levels at final on treatment measurement: -66% versus -5% respectively). IGF-1 mean levels were significantly lower than placebo at all post baseline time points except the final on treatment measurement. Although, the trend of lower IGF-1 in the intervention group was still apparent at this time (change in mean IGF-1 levels at final on treatment measurement: -39% versus -5% respectively).

The magnitude of change and final mean GH levels and IGF-1 levels were similar in the intervention group of both trials.

With regard to patient status, the mean GH and IGF-1 levels at the end of the octreotide sc treatment periods were above the upper limit of a normalised level (<2μg/l for GH, <1.9-2.2U/ml for IGF-1) in both trials.

The mean levels of GH and IGF-1 do not give an indication of the number and degree of response from individual patients. The number of patients responding to treatment was only obtainable for the trial by Fredstorp and colleagues. In the treatment group GH levels were reduced to normal in 40% of patients. IGF-1 levels were also normalised in 40% of patients. Only 20% of patients in the intervention group achieved a normalised level for both markers. Corresponding values for the placebo group were not reported. Using other thresholds to gauge response revealed that 80% of octreotide sc treated patients had a reduction in GH of >50% of baseline, compared to 0% in the placebo group. The percentages were the same for patients attaining a >20% reduction in IGF-1.

No significant changes or treatment effects were observed in other biochemical markers or physical measurements measured in these studies. Neither trial reported any patient centred outcomes.

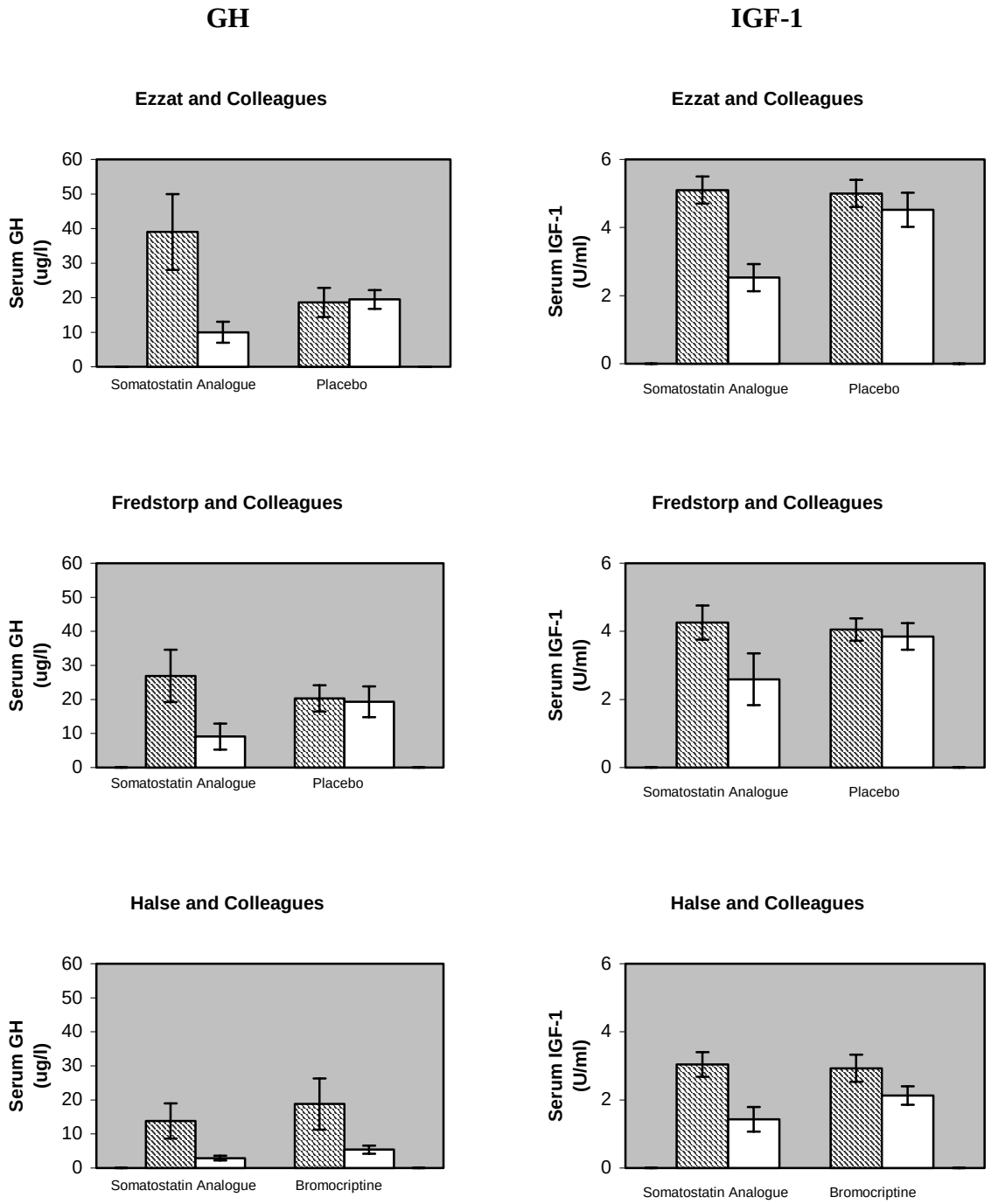
Adverse events were greater in the intervention groups than placebo groups and were predominantly gastrointestinal (diarrhoea/discomfort). 70-90% of patients assigned to intervention groups reported gastrointestinal problems compared to 10-30% in the placebo groups. Gall bladder examination and function were either not assessed or not reported for the placebo-controlled phase of these trials, but were for the open phase of the trial by Ezzat and colleagues.

5.1.3.2 Bromocriptine Controlled Trial

The trial by Halse and colleagues reported a statistically significant benefit of both octreotide sc and bromocriptine on mean GH and IGF-1 levels, but no statistical comparison was undertaken between the two groups.

The magnitude of the reduction in GH (-74% and -73% respectively) and IGF-1 (-54% and -27% respectively) were similar in each group (Figure 1).

Figure 1 - Serum GH and IGF-1 Before (shaded bars) and After (open bars) Interventions: somatostatin analogues as adjuvant treatment



(mean ±SEM)

At the end of treatment, mean GH levels were not normalised in either group. However, the mean IGF-1 level in the octreotide sc treated group did reach normalisation and was borderline for normalisation in the bromocriptine treated group. It is worth mentioning that compared to the other included trials, baseline levels of mean GH and IGF-1 were lower in this trial and this may suggest that the patients in this trial had comparatively less severe acromegaly. This may account for these normalised mean levels.

With regard to individual patient response, around 80% of patients in both groups had a reduction in GH of >50% of baseline. A similar percentage of the octreotide sc group and 60% of patients in the bromocriptine group had a reduction in IGF-1 of >20% of baseline. In some patients, there was only a limited or no response in the primary outcomes. The rates for GH were 17% for octreotide sc and 18% for bromocriptine and for IGF-1, 17% and 36% respectively.

Although the sample size was very small (n=23), sufficient information was available to calculate odds ratios for the comparison of octreotide sc and bromocriptine using normalisation of mean GH and/or IGF-1 as outcomes (Table 1). The odds ratios for both normalisation of GH and IGF-1 tend to favour treatment with octreotide sc over bromocriptine, however the 95% confidence intervals and P values suggest that the difference between the two treatments for either outcome was not statistically significant.

Table 1 - 2x2 tables of patient status with regard to normalisation of mean GH (left) and IGF-1 (right) serum concentrations after treatment with Octreotide sc and Bromocriptine

GH	Treatment	
	Octreotide sc	Bromocriptine
GH Normal (<2µg/l)	4	2
GH Elevated (>2µg/l)	8	9
Odds Ratio (95%CI)	2.25 (0.32-15.76)	
P value (Fisher's Exact Test)	1-tailed: 0.365 2-tailed: 0.640	

IGF-1	Treatment	
	Octreotide sc	Bromocriptine
IGF-1 Normal (<1.9U/ml)	8	4
IGF-1 Elevated (>1.9U/ml)	4	7
Odds Ratio (95%CI)	3.50 (0.63-19.50)	
P value (Fisher's Exact Test)	1-tailed: 0.150 2-tailed: 0.220	

Raw data taken form the trial by Halse and colleagues.[36] Odds ratios, confidence intervals and P values were calculated by the reviewers.

Patient centred outcomes were measured and reported for this trial. A significant and similar benefit of both octreotide sc and bromocriptine on soft tissue swelling as measured by a decrease in ring size was identified. Patient rated perception of their own symptoms also improved significantly and by a similar amount (30%) in both octreotide sc and bromocriptine treated patients, with a greater trend to improvement in headache, pain and vitality in the octreotide sc treated patients.

Tolerance was reported as being significantly better with octreotide sc treatment.

Adverse events were described as common and gastrointestinal in both groups but reported in only limited detail. Constipation was reported as common in the bromocriptine treated patients and diarrhoea in the octreotide sc treat patients.

5.1.4 Discussion

The effectiveness of octreotide sc as an adjuvant therapy to surgery or radiotherapy in the treatment of acromegaly has been evaluated in a small number of trials, which enrolled a relatively small number of patients. The trials contained methodological weaknesses, which included short duration of treatment period/follow up, lack of measurement of patient centred outcomes, incomplete reporting of the results and incomplete statistical analysis.

The studies suggest that octreotide sc is more effective than placebo and equally as effective as bromocriptine in reducing serum GH and IGF-1. The degree of octreotide sc benefit on mean GH and IGF-1 was consistent across the placebo and bromocriptine controlled trials. Not all patients appear to respond to octreotide sc treatment. The same is true for treatment with bromocriptine. Therefore, on the limited evidence these drugs could be classed as inter-changeable.

The non-statistically significant trend towards higher rates of normalisation of systemic GH and IGF-1 with octreotide sc compared to bromocriptine (Table 1) warrants further research. This research should address the issues above in addition to recruiting as many patients as possible. No controlled trial has evaluated the effectiveness of other dopamine agonists, and in particular cabergoline, compared to somatostatin analogues. Robust research with sufficient power is required in this area as currently cabergoline is often used and bromocriptine rarely (Daggett P, Stafford General Hospital, Stafford, UK; Stewart P, Department of Medicine, University of Birmingham, UK: personal communications, 2000).

The relatively short duration of the included studies would have been insufficient to detect long term benefits, long term adverse events (in particular gall stone formation), and long term compliance.

The effectiveness of depot preparations of somatostatin analogues as adjuvant treatment to surgery / radiotherapy has not been assessed by controlled trials.

None of the included trials studied a combined treatment of somatostatin analogues and dopamine agonists against the individual preparations. Although the mechanism by which dopamine agonists act in acromegaly is not totally clear it is likely to be different from somatostatin analogues. Further trials are required to assess whether combination therapy has greater efficacy than each treatment singularly.

5.1.5 Key Points: Somatostatin analogues as adjuvant treatment

- Two RCTs compared somatostatin analogue (octreotide sc) to placebo. One RCT compared somatostatin analogue (octreotide sc) to dopamine agonist (bromocriptine)
- A proportion of the patients in these trials had not undergone treatment with surgery or radiotherapy
- Measurement of systemic concentrations of GH and IGF-1 were the primary outcomes in all three trials
- All three RCTs are of relatively short duration and two enrolled relatively small numbers of patients
- Octreotide sc appears to be more effective than placebo
- From the limited evidence octreotide sc appears equally as effective as bromocriptine

- Not all patients appear to respond to treatment with octreotide sc
- Based on the limited evidence octreotide sc is as efficacious as bromocriptine
- No trials were found on octreotide LAR or lanreotide LA compared to any other medical treatment, placebo or no treatment as adjuvant treatment in acromegaly.
- The effectiveness of cabergoline compared to somatostatin analogues as adjuvant treatment has not been assessed by RCT
- Further robust research is required:
    i. to clarify whether octreotide sc is more effective than bromocriptine
    ii. to compare the effectiveness depot preparations of somatostatin analogues (octreotide LAR, lanreotide LA) with dopamine agonists
    iv. to compare the effectiveness of cabergoline with that of somatostatin analogues
    iii. to determine the effectiveness of combined treatment with somatostatin analogues and dopamine agonist compared to single drug therapy

5.2 Primary Treatment, Neo-Adjuvant Treatment and Analogue Comparison

Initially 229 references were identified by the formal search and scrutinised (Appendix IX). 171 were immediately rejected on the basis of information in the title or abstract. 58 hard copies were obtained either because a decision could not be made due to insufficient information or because the studies were potentially relevant for inclusion. Part translations were obtained of 2 articles (French/Czechoslovakian) to facilitate making a decision. 27 papers were immediately rejected as irrelevant based on information contained within the previously unseen abstracts and the remaining 31 papers were divided where relevant to the three questions. Some papers were relevant to more than one question. The specific inclusion and exclusion criteria were applied to these subgroups.

5.2.1 Primary Treatment

5.2.1.1 Quantity and Quality of Research Available

Of the 14 papers relevant to the use of somatostatin analogues as a primary treatment for acromegaly, none adhered to all the inclusion criteria. The predominant reason for exclusion was non-adherence to the criterion specifying population. A small number did not meet the criterion for study design. A list of excluded papers, including the reason for exclusion, can be found in Appendix VIII. There were no disagreements between reviewers when included studies were crosschecked for correct application of the inclusion criteria.

5.2.1.2 Discussion

Given that no studies met the inclusion criteria, it is evident that the use of somatostatin analogues as a primary treatment for acromegaly has not been investigated by RCT. Therefore, due to lack of robust evidence it is not possible at this time to determine whether somatostatin analogues are an effective first line treatment for acromegaly. A definitive answer will only be possible by undertaking well controlled RCTs powered to detect the effectiveness of somatostatin analogues compared to surgical resection of the pituitary tumour in newly diagnosed patients who have not undergone any previous treatment for acromegaly. Such a study may never be undertaken for ethical reasons related to the withholding of surgical treatment. For patients with inoperable tumours or

where surgery is contraindicated radiotherapy is the treatment of choice with dopamine agonists and or somatostatin analogues as adjuvant treatment. Trials may be possible where radiotherapy is also contra-indicated or rejected by the patient, although patient numbers are probably too small to warrant such a study.

As already stated the primary reason for exclusion of studies was that the study population did not totally consist of patients with previously untreated acromegaly and this was the sole reason for exclusion in a number of trials. Stratification of patients at randomisation with regard to previous treatments would have given rise to useful data but was not undertaken by any of the trials. Such stratification should be considered in future trials where the patient population has undergone a spectrum of previous treatments.

5.2.1.3 Key Points: Somatostatin analogues as primary treatment

- No RCTs have specifically evaluated the effectiveness of somatostatin analogues as a primary treatment for acromegaly
- Trials may be deemed unethical with regard to most acromegaly patients, as the aim of the main comparators (surgery, radiotherapy) is to cure rather than to control symptoms.

5.2.2 Neo-Adjuvant Treatment

5.2.2.1 Quantity of Research Available

Of the 14 papers relevant to the use of somatostatin analogues as neo-adjuvant treatment in acromegaly prior to tumour resection, 4 papers comprising reports of 2 RCTs met the inclusion criteria. The main reason for exclusion was non-adherence to the criterion for study design. A list of included and excluded papers, including the reason for exclusion can be found in Appendix VIII. There were no disagreements between reviewers when included studies were cross-checked for correct application of the inclusion criteria.

5.2.2.2 Characteristics and Quality of Included Studies

Detailed information on the characteristics and methodological quality of the included studies is tabulated in Appendix XI. The key features of these tables are described below.

The RCT by Ezzat and colleagues[a] compared four months of treatment with octreotide sc (3 x daily) prior to surgical resection of a pituitary tumour to immediate resection of the tumour[37-39]. The RCT by Zgliczynski possessed a similar design except that lanreotide (LA) was the analogue employed and the duration of treatment was 3 months[40]. In both studies dose regimes were within ranges specified in the BNF.[22] The route of surgery was only stated in the trial by Zgliczynski and was by the transphenoidal route. As far as reported, the population of acromegaly patients included in each study possessed relatively similar characteristics, although patients with micro-ademomas, were excluded from the study by Ezzat and colleagues. Patient numbers were small with 86 in the trial by

[a] This appears to be a different trial to the trial by the same lead author included in sections 3.2.1.2-4 on somatostatin analogues as adjuvant treatment in acromegaly.

Ezzat and colleagues and 50 in the trial by Zgliczynski. The major outcomes measured by both trials were serum GH and IGF-1 and the trial by Ezzat and colleagues also reported on the morphological characteristics of excised tumours. Neither study measured any patient centered outcomes. The length of patient follow up after surgical resection of their tumour was short at only one month in the trial by Ezzat and colleagues and was not stated in the other trial.

The quality of the trials as assessed using the Jadad scale was poor (1) in the case of the trial by Zgliczynski and only slightly better (2) in the trial by Ezzat and colleagues. Lack of clarity or omission of details resulted in an inability to assess many features of both trials. In the case of the trial by Zglinczynski these omissions may be due to the publication format. Our efforts to contact this trialist for further information have not been successful. On the whole, both trials possessed similar characteristics as both were essentially of open design and with investigators blinded for selected outcomes. The methods of randomisation and concealment of allocation were unclear, as were any differences in patient characteristics between groups of the same trial. Follow up rates were difficult to establish.

In the trial by Ezzat and colleagues some patients appear to be missing from the analysis, and not all outcomes were measured for all patients. The criteria by which patients were selected for specific outcome measurements were unclear. With regard to the morphological and histological analysis of excised tumours, samples showing signs of major membrane damage were excuded from any analysis, however the numbers excluded were not stated. Sub-group analysis of these tumour samples was confined to densely and sparsely granulated tumours. Given the selection of samples it is clear that the findings of the morphological and histological analysis may not be representative. The results of the trial by Zglicznski were not fully reported. The analysis of results was not complete in either of the trials, as statistical comparison between groups was not undertaken.

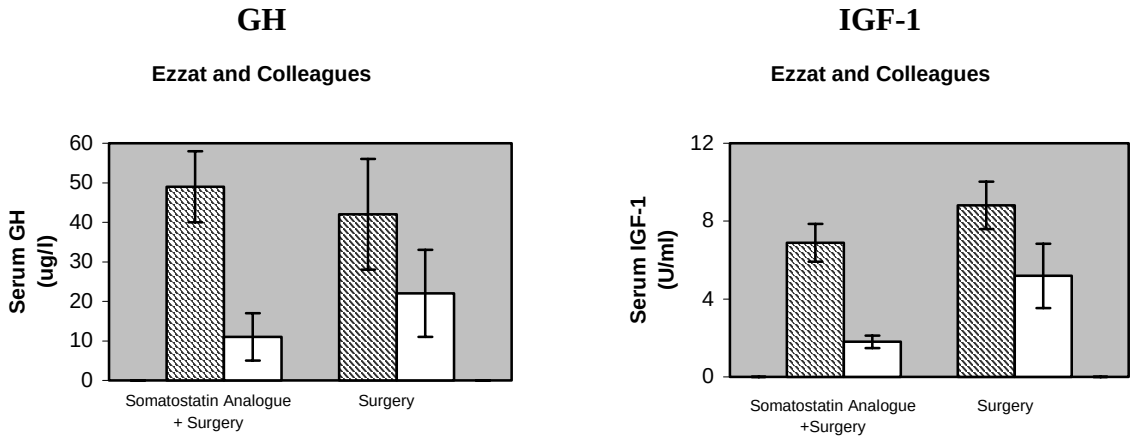
5.2.2.3 Evidence about Effectiveness

Detailed information on the evidence of effectiveness from the included studies is tabulated in Appendix IX. The key features of the table are described below.

Ezzat and colleagues reported a significant beneficial reduction in both mean serum GH and IGF-1 in both the combined octreotide sc/surgery group and surgery only group over baseline at one month post surgery. The change in both markers appeared to be greater in the combined treatment group (change: GH -78%; IGF-1 -74%) than the surgery only arm (change: GH -48%; IGF-1 -41%) although no analysis comparing groups was undertaken (Figure 2). These outcomes were only reported for 80% of the study population and therefore a degree of uncertainty exists around these findings. Details on the number of patients with normalised GH and or IGF-1 levels were not given.

Mean GH and IGF-1 data were not reported in the trial by Zgliczynski, although it was reported that a significantly greater proportion of patients who underwent combined treatment were classed as cured than the patients treated by surgery only (76% & 44% respectively). However, what constituted a cured state was not defined.

Figure 2 - Serum GH and IGF-1 Before (shaded bars) and After (open bars) Interventions: Somatostatin analogues as neo-adjuvant treatment prior to tumour resection



(mean ±SEM)

With regard to the effects of treatment on tumour morphology neither trial presents unambiguous results due to the uncertainty surrounding tumour selection in the trial by Ezzat and colleagues and the absence of data in the trial by Zglicznski.

5.2.2.4 Discussion

Although both trials indicate a trend towards greater benefit from combined treatment, weaknesses in their design and reporting precludes determining whether neo-adjuvant treatment with somatostatin analogues improves the outcome of tumour resection surgery in patients with acromegaly. Trials with more robust design and reporting are required. Patient centred outcomes should also be measured.

5.2.2.5 Key Points: Somatostatin analogues as neo-adjuvant treatment

- Two RCTs have been undertaken on the effectiveness of somatostatin analogues as a neo-adjuvant treatment to surgical resection of a pituitary tumour compared to immediate surgery
- One trial employed octreotide sc and the other lanreotide LA
- The quality and reporting of both trials was poor
- It is not possible to determine whether neo-adjuvant treatment with somatostatin analogues improves the outcome of tumour resection surgery in patients with acromegaly due to lack of robust evidence

5.2.3 Comparison Between Somatostatin Analogues

5.2.3.1 Quantity of Research Available

Of the 16 papers potentially relevant to the comparison of somatostatin analogues only one study met the inclusion criteria. The main reason for exclusion was non-adherence to the criterion for study design.

The two reviewers responsible for applying and crosschecking correct application the inclusion criteria consulted a third reviewer with regard to the decision pertaining to a conference abstract.[41] After discussion, all accepted that the abstract should be excluded from the review as it did not adhere to the criterion for study design.

A list of excluded studies including the reason for exclusion can be found in Appendix VIII.

5.2.3.2 Characteristics and Quality of Included Studies

Detailed information on the characteristics and methodological quality of the included trial by Chanson and colleagues[42] is tabulated in Appendix IX[b]. The key features of these tables are described below.

The included study was a two-phase trial. The first phase was a multicentre open labelled RCT that compared lanreotide LA treatment with octreotide LAR. The second phase was a randomised dose range trial of octreotide LAR only. Only the first phase is relevant to this review.
In this first phase the dose regimes were within ranges specified in the BNF.[22] The sample size at 125 was large compared to other acromegaly trials. All the patients had previously been treated for 2-117 months with lanreotide LA. 27 patients were enrolled in the lanreotide LA treatment group and 98 in the octreotide LAR group as this group was powered for the second phase of the trial. The duration of treatment was short at only 3 months. The major outcomes measured were GH and IGF-1 levels.

The methodological quality of the trial using the Jadad scale was poor (1). From the description of the randomisation procedure, it is not clear whether allocation was adequately concealed. No information was given on which to assess whether differences existed between the groups at baseline. Although the number of withdrawals from the trial were stated, insufficient information was given to determine to which group these patients were allocated to and when they dropped out of the study. Furthermore, data on clinical efficacy and endocrine outcomes were excluded from analysis where the study protocol was not adhered to. Information on number and allocation of exclusions were not given. Data on combined withdrawals and exclusions for biochemical outcomes in the first phase of the study were available and indicated that the follow up rates were similar for both groups at around 80%.

[b] This trial was initially identified from a poster presented at the 6th International Pituitary Conference (Long Beach, California, USA, June 15-17 1999). On contacting the lead author we were provided with a copy of a full report of the study that had been submitted for publication. It was on this copy that we based our assessment and it was this version of the report that was subsequently published as cited above.

Analysis of results was not complete as statistical comparison between both treatment groups was not undertaken for the first phase of the trial.

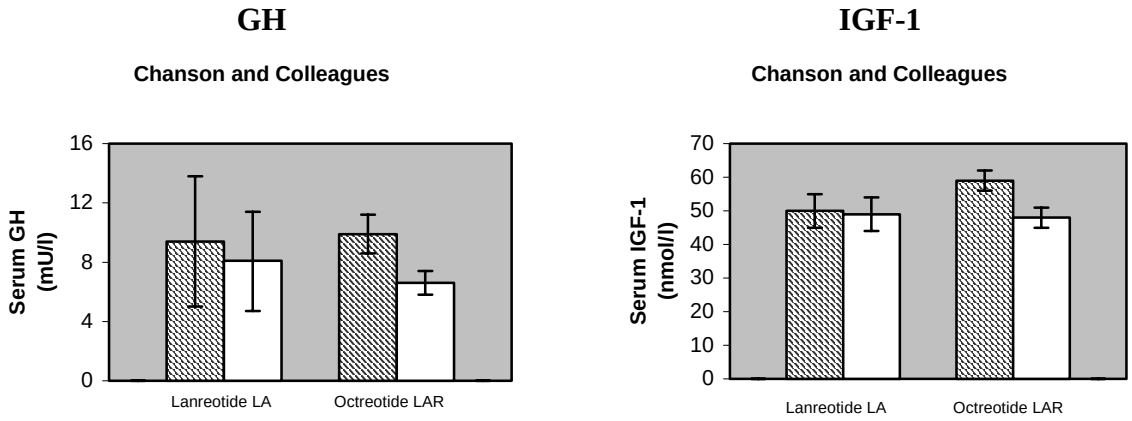
Many of the outcomes measured were not reported solely for the first phase of the trial. For many outcomes data from the octreotide LAR treated patients in the first and second phases were pooled for comparison with data from the lanreotide LA treated patients in the first phase, potentially introducing bias. We have only presented the available data from the first phase of the trial in this review.

5.2.3.3 Evidence about Effectiveness

Detailed information on the evidence of effectiveness from the included study is tabulated in Appendix IX. The key features of the table are described below.

A greater reduction in mean GH and IGF-1 was measured in the octreotide LAR (-33% and -19% respectively) than the lanreotide LA (-14% and -2% respectively) treated group. The change in the lanreotide LA group was not significant and the statistical analysis was not reported for the octreotide LAR group or for comparison between groups (Figure 3). Mean GH and IGF-1 levels were not reduced to normal levels in either group. The proportion of patients with normal IGF-1 levels increased from baseline in the octreotide LAR but not the lanreotide LA treatment groups.

Figure 3 - Serum GH and IGF-1 Before (shaded bars) and After (open bars) Interventions: Comparison between somatostatin analogues



(Mean ±SEM)

No significant changes from baseline measurements were reported for other outcomes in either group.

Withdrawals and adverse events were not all described by study phase in this trial[c] and therefore it is impossible to identify all that occurred during the phase comparing octreotide LAR with

[c] More detailed information on adverse events was given in the initial conference poster presentation of the results of this trial (see footnote b), but omitted from the full publication.

lanreotide LA. Furthermore, the rates of adverse events may have been influenced by the design of the trial (see discussion below).

Throughout the whole two phase study, serious adverse events accounted for the withdraw of two patients on octreotide LAR, and were present in two patients, one on each analogue, who completed treatment. The events in the latter two patients were gastrointestinal. Furthermore, about 50% of all patients treated with each analogue experienced at least one adverse event. Most of these adverse events were described as mild and reversible. Injection site events occurred in less than 20% of patients with either analogue and were described as mild to moderate.

5.2.3.4 Discussion

For reasons related to the design of this trial, the findings cannot be totally relied upon to give dependable and generalisable information on the efficacy of one long acting analogue over the other. First, there are potential biases around the selection of patients. As all the patients were being treated with lanreotide LA at enrolment, the patients could be perceived as responders to lanreotide LA. However, it is not clear whether prior to initiation of lanreotide LA the patients were treated with octreotide sc to ascertain their response to somatostatin analogues. If so then the patients could represent an octreotide sc sensitive population. Second, octreotide LAR was always given after lanreotide LA and without a washout period. The possibility of effects related to carryover of lanreotide LA into the octreotide LAR treatment period cannot be ignored. The trialists acknowledge this point and comment that although the design may have influenced subjective assessments (symptoms/adverse events), the primary outcomes (GH and IGF-1) were not measured until three months after change from lanreotide LA to octreotide LAR. However, this delay would not compensate for effects which were not fully reversible or where the period to full reversibility was longer than, say, a few days. One such effect might be tumour shrinkage. Measuring primary outcomes and tumour size periodically during the three-month treatment period may have provided information to address these issues.

These factors may have an impact on the generalisability of both the reported efficacy and the rates of adverse events to the wider acromegalic population. The existence of this trial should not be used as the sole reason for prescribing patients octreotide LAR over lanreotide LA.

The flaws inherent in this study mean that there is insufficient reliable evidence to indicate whether any differences exist in the efficacy of one long acting analogue over another. Robust trials are required in this area. In the meantime, when initially prescribing a long acting analogue the choice of analogue should take into account factors such as frequency of dose and likely patient compliance. Furthermore, as somatostatin receptor subtypes have different affinities for octreotide and lanreotide and as the density of subtypes may vary from tumour to tumour, patients may be more responsive to one analogue than another.

No RCTs have looked at the efficacy of short acting octreotide sc given three times daily compared to either of the long acting analogues (octreotide LAR, lanreotide LA). For pragmatic reasons, patient and clinician preference is likely to favour the long acting analogues in those patients who respond to test doses with octreotide sc.

5.2.3.5 Key Points: Comparison between somatostatin analogues

- Only one RCT has compared the effectiveness of different somatostatin analogues, and this compared the depot preparations of octreotide LAR and lanreotide LA
- Weaknesses in the study design and reporting mean that the findings of this RCT cannot be relied upon to give dependable information on the effectiveness of one analogue over the other.
- The effectiveness of octreotide sc compared to depot somatostatin analogue preparations (octreotide LAR, lanreotide LA) has not been assessed by RCT
- No reliable evidence exist from RCTs on which to make a recommendation of one somatostatin analogue over another. Choice of depot analogue preparation should therefore be based on other factors.

6 ECONOMIC ANALYSIS

6.1 Cost Effectiveness Review

No published cost effectiveness studies on somatostatin analogues in the treatment of acromegaly were identified. A cost effectiveness analysis of treatment option using data from a convenience sample of patients with acromegaly was identified through searching conference abstracts.[43] One article arising from this analysis has since been published and this is essentially a cost study[44]. A second article arising from this analysis has been submitted for publication. Although we have copy of this article, we have been asked by the authors not to quote details from it as it has yet to be accepted for publication. Other articles detailing some costs and benefits of treatment options in acromegaly have been published.[45,46] A cost effectiveness analysis of the management of asymptomatic pituitary microadenomas, although considering acromegaly, does not specifically target nor report findings for this disease and does not consider somatostatin analogues.[45] A report on treatment options for acromegaly details potential costs of treatment with surgery, radiotherapy octreotide sc and bromocriptine, from the perspective of the Australian health care system.[46] There is no clear indication in this report on how costs were calculated. Other than drug costs, components for drug delivery, medical consultation and monitoring for adverse events may or may not have been taken into account. The costs per annum for treatment with octreotide sc were reported as AUS$22,025 (£8,810) and for treatment with bromocriptine were AUS$3,000 (£1,200). These values were calculated using 1996 prices.

6.2 Economic Evaluation

The economic evaluation concentrated on somatostatin analogues as adjuvant treatment to surgery and or radiotherapy.

6.2.1 Costs

To place identified strategies of adjuvant treatment in an economic setting, summary costs per patient per year of treatment using either somatostatin analogues or dopamine agonists were estimated. The strategies and resource requirements were identified by dialogue with endocrinologists treating patients with acromegaly. There are two strategies for treatment with somatostatin analogues, based on an initial two week test for responsiveness using octreotide sc then 3 months of treatment with depot preparations of either lanreotide (LA) or octreotide (LAR) at a set dose, followed by specific dose modulation based on patient requirement. There are also two strategies for treatment with dopamine agonists as both bromocriptine or cabergoline can be used clinically. Unlike somatostatin analogues, treatment strategies with dopamine agonists tend to be less complex, with the only major progression in treatment being the adjustment of dose to the patients needs. With all the strategies continuation of treatment into the second year follows the regime at the end of the first year. The resource requirements for the treatment strategies for the first and second year of treatment are outlined in Table 2. The unit costs of drugs, personnel and equipment are outlined in Appendix X in GB£.

Table 2 - The resource requirements for the first and second year of treatment with somatostatin analogues or dopamine agonists.

	Type of Resource	Treatment			
		Somatostatin Analogues		Dopamine Agonists	
		Octreotide	Lanreotide	Bromocriptine	Cabergoline
0-2weeks	Drug	Octreotide sc 150µg (100-200) 3xdaily	Octreotide sc 150µg (100-200) 3xdaily	Bromocriptine 20mg (10-30) daily	Cabergoline 1.75mg (1-4.5) weekly
	Administration	By Patient sc Injection Kits 3/day Training of patient in self administration of sc injection x1	By Patient sc Injection Kits 3/day Training of patient in self administration of sc injection x1	By Patient orally	By Patient orally
	Appointments	Out-patient x1	Out-patient x1	None	None
	Monitoring	IGF-1 test x1 Ultra-sound scan of gall bladder x1	IGF-1 test x1 Ultra-sound scan of gall bladder x1	None	None
2-14 weeks	Drug	Octreotide LAR 20mg every 28days	Lanreotide LA 30mg every 14 days	Bromocriptine 20mg (10-30) daily	Cabergoline 1.75mg (1-4.5) weekly
	Administration	Staff Nurse im injection x1	Staff Nurse im injection x 2	By Patient orally	By Patient orally
	Appointments	Out-patient x1	Out-patient x1	Out-patient x1	Out-patient x1
	Monitoring	IGF-1 test x1	IGF-1 test x1	IGF-1 test x1	IGF-1 test x1
Weeks 15-52	Drug	Octreotide LAR 20mg (10-30) every 28 days	Lanreotide LA 30mg every 10 days (7-14)	Bromocriptine 20mg (10-30) daily	Cabergoline 1.75mg (1-4.5) weekly
	Administration	Staff Nurse im injection x 9.5	Staff Nurse im injection x 26.6 (19-38)	By Patient orally	By Patient orally
	Appointments	Out-patient x2	Out-patient x2	Out-patient x2	Out-patient x2
	Monitoring	IGF-1 test x2 Ultra sound scan of gall bladder	IGF-1 test x2 Ultra sound scan of gall bladder	IGF-1 test x2	IGF-1 test x2
Weeks 53-104	Drug	Octreotide LAR 20mg (10-30) every 28 days	Lanreotide LA 30mg every 10 days (7-14)	Bromocriptine 20mg (10-30) daily	Cabergoline 1.75mg (1-4.5) weekly
	Administration	Staff Nurse im injection x 13	Staff Nurse im injection x 36.4 (26-52)	By Patient orally	By Patient orally
	Appointments	Out-patient x3	Out-patient x3	Out-patient x3	Out-patient x3
	Monitoring	IGF-1 test x3 Ultra sound scan of gall bladder x2	IGF-1 test x3 Ultra sound scan of gall bladder x2	IGF-1 test x3	IGF-1 test x3

It is important to note that Ipsen Ltd is able to supply Lanreotide LA under a cost assured scheme whereby the drug is supplied for a fixed monthly (28 day) cost irrespective of the dose required by the patient (Desson A, Ipsen Ltd, Maidenhead, UK: personal communication, 2001). At the time of this review the cost of this programme is equivalent to the cost of the low dose schedule of two 30mg doses every 28 days. This scheme is essentially a marketing tool, is widely available and has been in operation for some time. Therefore, it forms the basis for calculating the point estimate of

costs of lanreotide LA instead of other quoted prices.[22,47] No such scheme exists for octreotide sc or LAR.

The detailed costs of each strategy are given in Appendix X, and the point estimates of costs are summarised in Table 3.

Table 3 - Point estimates of costs (£)

	Somatostatin Analogues		Dopamine Agonists	
	Octreotide LAR	**Lanreotide LA**	**Bromocriptine**	**Cabergoline**
1-2 weeks	£537	£537	£20	£26
3-14 week	£2662	£2125	£222	£262
15-52 weeks	£8346	£6666	£582	£708
Total Year 1	£11,544	£9,328	£824	£996
Total Year 2	£11,471	£9,173	£824	£996

The cost for the first year of treatment with somatostatin analogues is £11,544 for octreotide LAR and £9,328 for lanreotide LA. Costs for dopamine agonists are approximately 10 times cheaper at £824 for bromocriptine and £996 for cabergoline. It is evident from these values that within class costs are similar.

Costs for the second year of treatment with each drug are not appreciably different to that for the first year.

Patients who have undergone pituitary irradiation require an annual 8 week withdrawal of treatment to assess residual disease activity. Medical treatment is resumed if GH/IGF-1 levels increase or signs and symptoms recur during this period. This period of withdrawal reduces second year point estimates to £9,766 for octreotide LAR and £7,831 lanreotide LA for these patients.

6.2.2 Sensitivity Analysis

A number of assumptions were made in determining the resource requirements of the strategies and the costs associated with each resource. These assumptions are outlined in Appendix X. Variability due to these assumptions have been incorporated into a sensitivity analysis to determine the uncertainty around the point estimates. The components of this analysis are highlighted below:

- The major variable considered to impinge on the point estimates is the dose of the interventions. The variation in dose of each intervention is outlined in Table 2 and Appendix X.
- Some of the costs associated with administration of treatment have been estimated from the National Schedule of Reference Costs[48] which also gives cost ranges for the interquartile 50% of NHS Trusts. These have also been incorporated.
- Finally, Ipsen Ltd provide a free nurse adviser service, which includes the availability of nurse advisers to give injections of lanreotide LA at a time and place convenient for the patient, thus removing the cost away from the NHS (Desson A, Ipsen Ltd, Maidenhead, UK: personal communication, 2001). No such scheme exists for octreotide sc or LAR.

Incorporating these elements into the analysis gives rise to the range of costs outlined in Table 4 for each of the treatment strategies.

Table 4 - Estimated variation in costs (£)

	Somatostatin Analogues		Dopamine Agonists	
	Octreotide LAR	**Lanreotide LA**	**Bromocriptine**	**Cabergoline**
1-2 weeks	394-672	394-672	10-30	15-68
3-14 week	2,644-2,672	2,091-2,135	145-291	176-520
15-52 weeks	6291-1,0384	6,561-6,715	359-790	458-1,514
Total Year 1	9,329-13,728	9,046-9,523	514-1,110	649-2,101
Total Year 2	8,655-14,264	9,024-9,234	514-1,110	649-2,101

Taking these uncertainties into consideration does not alter the findings from the point estimates that somatostatin analogues are much more expensive than dopamine agonists in both the first and second year of treatment. There is no overlap between the range of costs for these two classes of drug, with somatostatin analogues being between 4 and 28 times more expensive.

With regard to interclass variation, the range of costs for octreotide LAR is broader and has a much higher upper limit than that for lanreotide LA and this is primarily due to the fixed monthly price for lanreotide LA available through the cost assured scheme. If this scheme is not used the point estimate and range of costs for lanreotide LA would be £11,868 (9,046-15,874) for the first year and £12,649 (9,024-17,934) for the second year. This would put the values more in line with those for octreotide LAR, albeit with higher costs for those patients on larger doses of lanreotide LA.

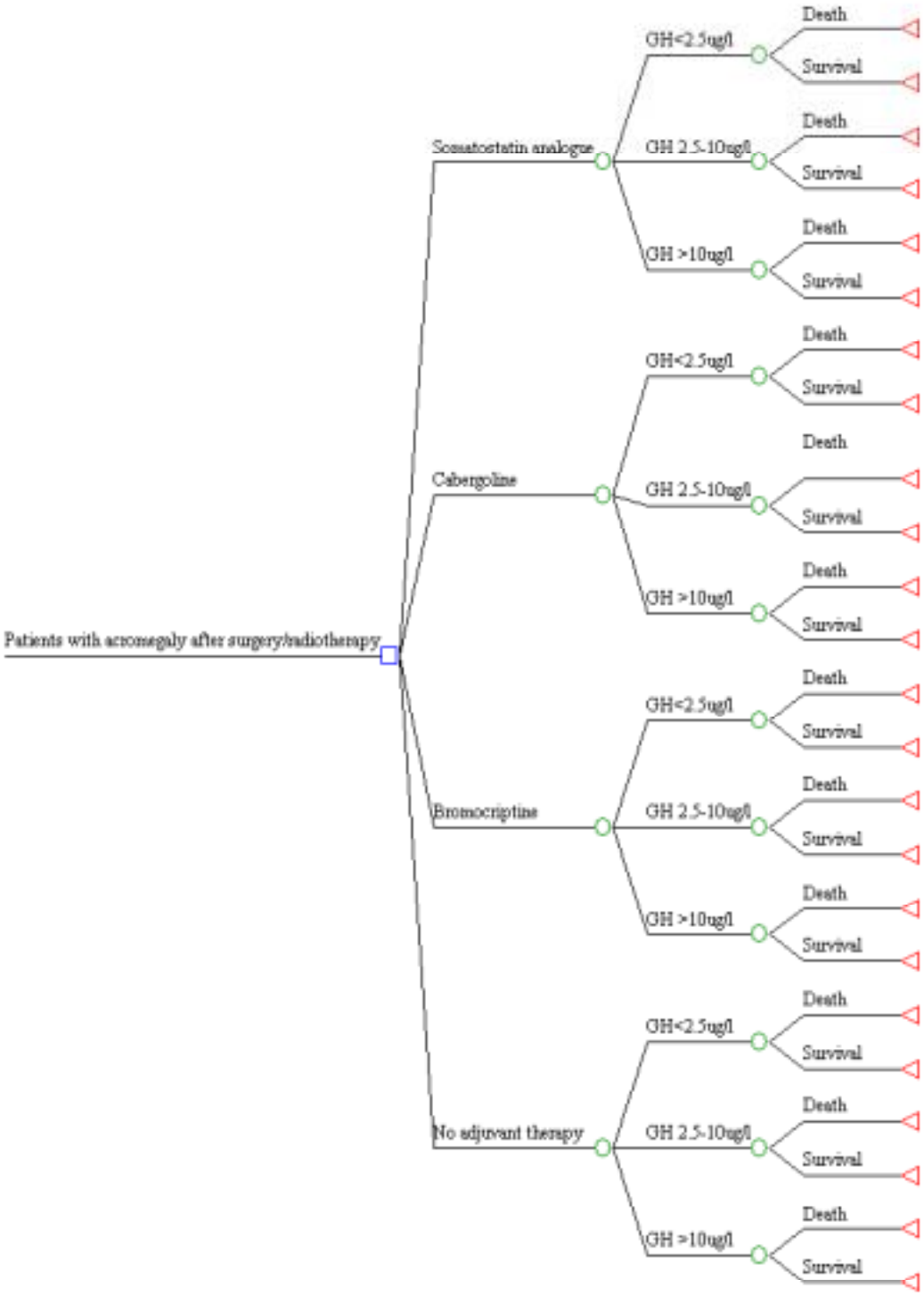
Given the potential saving to the NHS, clinicians treating patients with lanreotide LA at a dose of 30mg/14 days or greater should ensure that the drug is administered by the cost assured scheme. Furthermore, full use should be made of the free nurse adviser programme, provided by Ipsen Ltd for giving intra-muscular injections of lanreotide LA as this removes the cost from the NHS.

This cost analysis does not take into account situations where a shared care protocol exists. Existence of such protocols may require the transfer of skills from the outpatient clinic to general practice staff. However, the necessary training is likely to be brief and of negligible cost compared to the annual cost per patient.

6.3 Modelling

Given the limited evidence on effectiveness from the randomised controlled trials and the large cost difference between somatostatin analogues and dopamine agonists, decision analytic modelling was undertaken to give an indication of the incremental cost per life year gained and the incremental cost per QALY gained. The decision tree diagram for the model is shown in Figure 3 below.

Figure 4 - Decision tree framework on which modelling was based



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To populate this model data pertaining to efficacy of treatments, mortality and quality of life were predominantly obtained from cohort studies and / or estimated as outlined in Appendix X.

The outcome measure utilised was the frequency of final GH level in the three categories <2.5μg/l, 2.5-10μg/l and >10μg/l. The treatments categories compared were, no treatment, bromocriptine treatment, cabergoline treatment and somatostatin analogue treatment. Given the perceived similar efficacy of octreotide sc, octreotide LAR and lanreotide LA data on the efficacy of each of these was combined to give a class effect for all somatostatin analogues.

Population mortality data was estimated according to 1991-1995 data for the age range 40-45 years.[49] Standard mortality ratios for the different levels of GH were taken from the study by Orme et al[14]. Because of a lack of relevant randomised trials, the distribution of GH levels after each treatment was assumed based on several cohort studies. [21,50-58] Thus, it is important to note that the patients across these observational studies may or may not be comparable. As these studies often reported their findings in different GH categories, some assumptions were required. Furthermore, data on the efficacy of no treatment was taken from baseline values in the cohort studies. Given that many patients in these studies had undergone some form of medical adjuvant therapy prior to the collection of this data, the efficacy of no treatment may be over estimated in this analysis.

Treatment costs were as per the second year of treatment reported in the current systematic review except for the cost of no treatment, which was taken to be zero. We assumed that any other interventions given would be identical in all respects for all four groups and therefore need not be considered. Although we acknowledge that this may not be the case where additional treatment or care may be required to alleviate symptoms of acromegaly in the case of no treatment or to deal with adverse effects of active drugs. The second year costs for octreotide and lanreotide were averaged to give the costs for the somatostatin analogue group.

Translation of symptoms into QALYs had to be assumed given the limited empirical data available on quality of life.

Further information on the modelling can be found in Appendix X.

The incremental point estimates for cost per life year saved are reported in Table 5. The incremental cost per life year saved for somatostatin analogue over cabergoline is about £64.5 million.

Table 5 - Incremental Point Estimates of Cost per Life Year Saved (£)

Somatostatin Analogue	Cabergoline	Bromocriptine	No Treatment
15,179,412	1,859,944	4,847,059	Reference
18,623,529	470,588	Reference	
64,539,792	Reference		

The incremental point estimates for cost per QALY are reported in Table 6. As these estimates are based on subjectively assumed quality of life values they are even less accurate as those for life year saved which have a more empirical basis. The incremental cost per QALY saved for somatostatin analogues over cabergoline is £531,000.

Table 6 - Incremental Point Estimates for Cost Per QALY (£)

Somatostatin Analogue	Cabergoline	Bromocriptine	No Treatment
102,919	12,040	32,864	Reference
126,271	2,983	Reference	
530,900	Reference		

6.3.1 Sensitivity Analysis

In the incremental cost utility calculations, there is great uncertainty in the effectiveness estimates, the quality of life assumed and the costs. The likely range of these uncertainties is given in Table 7 and how they were derived is described below. The estimated uncertainty for the effectiveness data were driven by the range of frequency values in the cohort for the GH level <2.5µg/l category with the range for the other two categories calculated proportionally using the point estimates for the same categories, in order to ensure that the combined proportion of patients across three GH categories is 100%.

Table 7 - Range of variables used in sensitivity analysis of costs per life year gained and cost per QALY

GH Category	QALY Index	Frequency of GH Level after Treatment			
		Somatostatin Analogue	Cabergoline	Bromocriptine	No Treatment
<2.5µg/l	0.85-1.0	0.22-0.67	0.28-0.46	0-0.2	0-0
2.5-10µg/l	0.70-0.95	0.22-0.52	0.29-0.39	0.36-0.44	0.2-0.6
>10µg/l	0.50-0.80	0.11-0.26	0.25-0.33	0.44-0.56	0.4-0.8
Costs (£)		8,655-17,934	649-2,101	514-1,110	0-0

In the absence of any data the uncertainty around the quality of life estimate was itself assumed.

Uncertainty around costs was the same as those calculated in this report (see Table 4).

All these uncertainties were incorporated into a sensitivity analysis to give a range of incremental cost per life year saved and cost per QALY values (Tables 8 and 9 respectively). The analysis combined the uncertainties to give the most optimistic and most pessimistic estimates for these outcomes. For example, for the most pessimistic scenario, the lowest estimate of effectiveness was combined with the highest estimate of costs. For the most optimistic scenario, the highest estimate of effectiveness was combined with the lowest estimate of costs.

Table 8 - Estimated variation in Incremental Cost per life year saved (£)

Somatostatin Analogue	Cabergoline	Bromocriptine	No Treatment
12,601,922-23,759,936	1,571,048-2,992,451	9,448,529-3,886,555	Reference
1,287382-35,856,777	376,359-2,379,352	Reference	
29,251,005-300,436,433	Reference		

The sensitivity analysis indicates that the incremental cost per life year saved for somatostatin analogue over cabergoline lies between £29million and £300 million.

Table 9 - Estimated Variation in Incremental Cost per QALY (£)

Somatostatin Analogue	Cabergoline	Bromocriptine	No Treatment
111,769-127,115	14,179-15,439	23,111-126,772	Reference
110,940-180,796	3,236-11,255	Reference	
252,824-3,164,138	Reference		

The sensitivity analysis indicates that the incremental cost per QALY for somatostatin analogue over cabergoline lies between £250,000 and £3.2 million.

6.4 Key Points: Economic Analysis

- No cost utility analysis of somatostatin analogue treatment for acromegaly has been published
- Cost of treatment with somatostatin analogues per year are estimated to be £11,471 (range 8,655-14,264) with octreotide LAR and £9,173 (range 9,024-9,234) with lanreotide LA. The estimated costs for dopamine agonist are £824 (range 514-1,110) with bromocriptine and £996 (range 649-2,101) with cabergoline
- Although it is essentially a marketing tool, clinicians of patients treated with lanreotide LA at a dose of 30mg every14 days or greater should ensure that drug costs are met by the cost assured scheme. Similarly, patients treated with lanreotide LA should have injections administered by the free nurse adviser service also to remove this cost from the NHS. Similar schemes are not available for octreotide sc or LAR treated patients.
- Decision analytic modelling reveals that the incremental cost per life year saved for somatostatin analogue over cabergoline is £64.5M (range 29M-300M) and the incremental cost per QALY is £530K (range 253K-3.2M). These estimates are based on data from observational studies, or subjective assumptions.

7 CONCLUSIONS

The strengths of this systematic review are that there were clearly defined questions and a comprehensive search strategy. However, the small amount of RCT evidence identified limits the ability to answer questions about the effectiveness of somatostatin analogues and the undertaking of a detailed economic analysis. Specific conclusions are detailed below.

Adjuvant Treatment

The evidence from the two placebo controlled trials suggests that octreotide sc is an effective adjuvant treatment for acromegaly. A single RCT indicates that octreotide sc is as effective as bromocriptine. All three trials are of short duration, enrolled small numbers of patients (a proportion of these patients had not undergone surgical or radiotherapy treatment) and were of low methodological quality. On the limited evidence octreotide sc and bromocriptine could be classed as having similar efficacy. The effectiveness of other somatostatin analogue preparations compared to dopamine agonists as adjuvant treatment have not been assessed by RCT. Further research of robust design and with sufficient power is required particularly with regard to comparison with cabergoline as this appears to be the dopamine agonist most commonly used. No RCT has studied the effectiveness of combining dopamine agonist and somatostatin analogue treatment.

Primary Treatment

No RCTs have evaluated the effectiveness of somatostatin as primary treatment for acromegaly. Trials may be deemed unethical as the aim of the main comparator (surgery) is a cure. Trials may be possible on those patients for whom surgery and radiotherapy is contraindicated or has been refused by the patient, although the number of such patients may be too small to allow such studies.

Neo-Adjuvant Treatment

It is not possible to determine whether somatostatin analogues are effective as neo-adjuvant treatment due to methodological weaknesses and poor reporting from the two RCTs available. Further more robust research is required.

Analogue Comparison

Only one RCT has compared the effectiveness of different somatostatin analogues (octreotide LAR vs lanreotide LA). Weaknesses in study design and reporting mean that the findings of this trial cannot be relied upon to give dependable information on choice of depot preparation. Therefore when initially prescribing a long acting analogue the choice of analogue should take into account factors such as frequency of dose, likely patient compliance and response, and the cost of treatment.

The primary criterion separating the first three questions was that for study population. For the effectiveness of somatostatin analogues as a primary or neo-adjuvant treatment, trials containing mixed populations of patients with previous and no previous treatment for acromegaly were excluded from the review, and for adjuvant treatment the majority of the population had to have undergone surgery and / or radiotherapy. Thus, for the most part, trials on mixed populations would

have been excluded from this review. Patients were not stratified at randomisation for previous treatment in any of the trials that were excluded purely on the basis of non-adherence to population criterion. Future trials should stratify patients by previous treatments if enrolling a heterogenous population.

In the only relevant published cost study we identified, the costs of treatment with somatostatin analogues and dopamine agonists, and thus the cost differential between these treatments, were of the same order of magnitude to the cost study in this review.[46] Cost analysis shows that treatment with somatostatin analogues is 10 times more expensive than treatment with dopamine agonists (octreotide LAR £11,471/year, lanreotide LA £9,173, bromocriptine £824 cabergoline £996). Decision analytic modelling reveals that the incremental cost per life year saved for somatostatin analogue over cabergoline is £64.5M and £18.6M over bromocriptine and that the incremental cost per QALY is £531K over cabergoline and £126K over bromocriptine. Furthermore,it is unlikely that all patients will respond to one treatment. Thus non-responders to bromocriptine may be responders to cabergoline (and visa versa) and non-responders to dopamine agonist may be responders to somatostatin analogues (and visa versa) and some patients may have a greater response to one somatostatin analogue than another. As such, the cost impact on the NHS of adjuvant treatment after pituitary surgery and or radiotherapy in acromegaly is difficult to estimate with the current level of information. Given that a) octreotide sc and by assumption, somatostatin analogues in general appear to be an effective treatment for acromegaly and b) appear as effective as bromocriptine the following could be suggested: If there are no over riding reasons to choose either dopamine agonist or somatostatin analogues, then patients should initially be prescribed a dopamine agonist (ie bromocriptine), then if non responsive switched to the other dopamine agonist (ie cabergoline). If not responsive to this, treatment should progress to assessing responsiveness to somatostatin analogues. A similar strategy is employed in at least one centre (Stewart P, Department of Medicine, University of Birmingham, UK: personal communications, 2000).

Overall the quality of the available evidence is poor. Most trials are of short duration and many enrol few patients. The methodological quality and reporting are also generally poor. These factors limit the usefulness of the data. The choice of primary outcomes in this review (GH/IGF-1) reflects those reported in the included studies. This fixation on measuring GH and IGF-1 levels as primary outcomes is understandable as both are generally regarded as markers for the clinical severity of the disease, and from the clinicians perspective can be easily measured to assess responsiveness to treatment. However it is important that patient centred outcomes are not neglected as appears the case in these trials.

Short term duration of the included trials does not give information on long term maintenance of any benefits, the extent and duration of adverse events, occurrence of long term adverse events and patient compliance over years of treatment.

The lack of robust evidence on the effectiveness of somatostatin analogues in the treatment of acromegaly indicates the need for further quality research. This research should cover a number of comparisons with alternative treatments as outlined in the various sections of this review. Placebo controlled trials are no longer warranted on this topic due to the ethical issue around withholding treatment. Furthermore, any future studies should take account of the limitations of the current evidence base mentioned above.

This review only considered evidence from RCTs (and non-randomised controlled trials for adjuvant treatment). Evidence from less robustly designed studies was not considered. Given the

limited evidence from the included trials it is perhaps pertinent that evidence from less robust study designs be assessed in any future review on this topic.

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41 Pedroncelli,A, Lancranjan,I, Montini,M, Albani,G, Pagani,MD, Gianola,D, *et al.* The effects of different long-acting somatostatin analogues in the management of acromegaly. (Abstract) *Endo '99 - 81st Annual Meeting of The Endocrinology Society*
42 Chanson P, Boerlin V, Ajzenberg C, Bachelot Y, Benito P, Bringer J, *et al*. Comparison of octreotide acetate LAR and lanreotide SR in patients with acromegaly. *Clinical Endocrinology* 2000; **53**:577-586.
43 Wilson,L, Shin,J, Ezzat,S. Cost analysis of different therapeutic options in the management of acromegaly. (Abstract) *Endo '99 - 81st Annual Meeting of The Endocrinology Society*
44 Wilson LS, Shin J, Ezzat S. Longitudinal assessment of economic burden and clinical outcomes in acromegaly. *Endocrine Practice* 2001; **7**(3):170-180.
45 King,J, Justice,A, Aron,D. Management of incidental pituitary microadenomas: a cost-effectiveness analysis. *Journal of Clinical Endocrinology & Metabolism* **82**, 3625-3632.1997
46 Weekes LM, Ho KK, Seale JP. Treatment options in acromegaly. Benefits and costs. *Pharmacoeconomics* 1996; **10**(5):453-459.
47 Monthly index of medical specialities (MIMS). London: Haymarket Publishing Ltd; May 2001.
48 The National Schedule of Reference Costs. London: Department of Health; 2000.
49 National Statistics. Mortality Statistics - general. London: The Stationery Office; 1995. Report No.: 31.
50 Sassolas G, Harris AG, James-Deidier A. Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. French SMS 201-995 approximately equal to Acromegaly Study Group. *Journal of Clinical Endocrinology & Metabolism* 1990; **71**(2):391-397.
51 Newman CB, Melmed S, Snyder PJ, Young WF, Boyajy LD, Levy R, *et al*. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients--a clinical research center study [published erratum appears in J Clin Endocrinol Metab 1995 Nov;80(11):3238]. *Journal of Clinical Endocrinology & Metabolism* 1995; **80**(9):2768-2775.
52 Colao AM, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, *et al*. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *Journal Of Clinical Endocrinology And Metabolism* 2001; **86**:2779-2786.
53 Vance ML, Harris AG. Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide. Results of the International Multicenter Acromegaly Study Group. *Archives of Internal Medicine* 1991; **151**(8):1573-1578.

54 Chanson P, Leselbaum A, Blumberg J, Schaison G, the French Multicenter Study Group on Lanreotide in Acromegaly. Efficacy and tolerability of the long-acting somatostatin analog lanreotide in acromegaly. a 12-month multicenter study of 58 acromegalic patients. *Pituitary* 2000; **2**:269-276.
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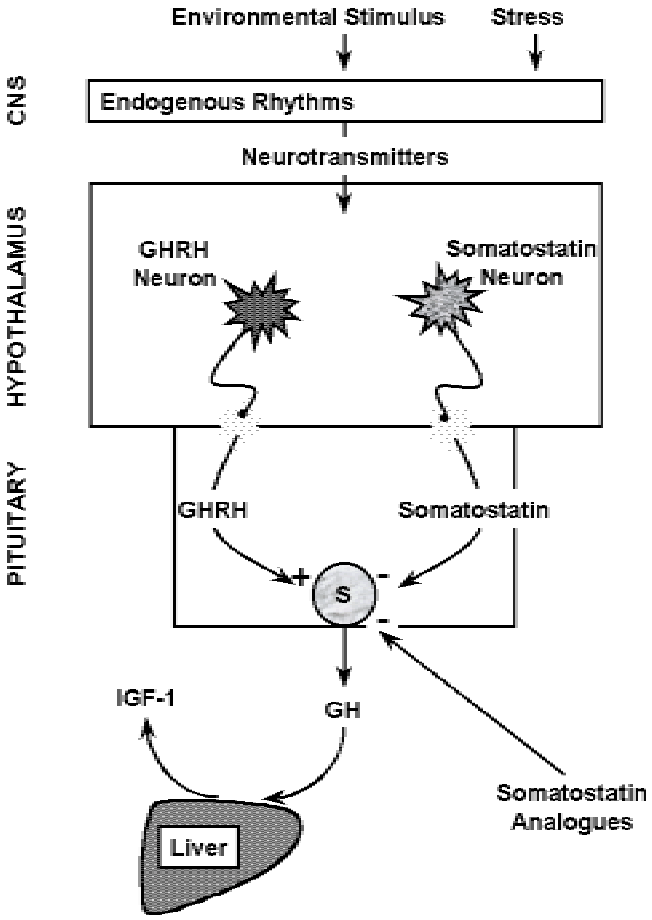
60 Netten A, Curtis L. Unit Costs of Health & Social Care. Canterbury: Personal Social Services Research Unit, University of Kent; 2000.

Appendix 1- Human Pituitary GH Secretion

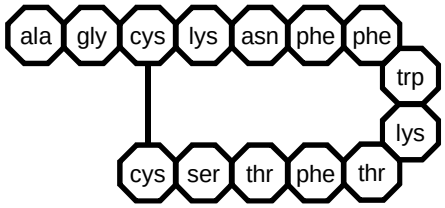


Schematic representation of human pituitary GH secretion.
The action of exogenous stimuli (stress, environmental) and endogeonous stimuli (circadian rhythms) the CNS, results in regulation of the hypothalamus. Stimulated GHRH neurons in the hypothalamus release GHRH which travels to the pituitary and stimulates somatotroph cells (S) to produce GH. Secreted GH acts on the liver to generate most of the circulating IGF-1. Stimulated somatostatin neurons within the hypothalamus release somatostatin, which acts via somatostatin receptors on the surface of the somatotrophs to inhibit the secretion of GH. A number of feedback mechanisms exist (not shown) by which GH secretion is regulated by the action of GH and IGF-1 on somatotroph cells, somatostatin neurons and GHRH neurons. Somatostatin analogues act directly on somatotroph cells and mimic native somatostatin thus inhibiting the secretion of GH, and ultimately IGF-1.

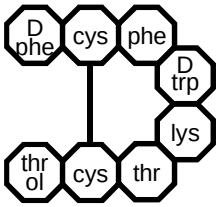
Adapted from: Casanuena F. Physiology of growth hormone secretion and action. Endocrin. Metab Clin N Amer. 1992; 21(3):483-517.

Appendix 2 - Schematic Representation of the Structure and Amino Acid Composition of Somatostatin and Somatostatin Analogues

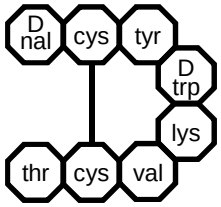
Somatostatin



Octreotide



Lanreotide



Adapted from: van der Lely AJ, de Herder WW, Lamberts SW. A risk-benefit assessment of octreotide in the treatment of acromegaly. Drug Safety 1997; 17(5):317-324.

Appendix 3 - Search Strategies

A. Clinical Effectiveness

MEDLINE 1966-2000 & CINAHL 1982-2000 (on OVID)

1	Randomized controlled trials.pt.
2	Randomized controlled trials.sh.
3	Random allocation.sh.
4	Double blind method.sh.
5	Single blind method.sh.
6	1 or 2 or 3 or 4 or 5
7	Animal.sh.
8	Human.sh.
9	7 not (7 and 8)
10	6 not 9
11	Clinical trials.pt.
12	Exp clinical trials/
13	(clin$ adj3 trial$).ti,ab.
14	((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
15	Placebos.sh.
16	Placebo$.ti,ab.
17	Random.ti,ab.
18	Research design.sh.
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	19 not 9
21	10 or 20
22	Acromegaly/ or “acromegaly”.mp.
23	Acromegal$.mp.
24	22 or 23
25	“OCTREOTID$”.mp.
26	“SMS 201-995”.mp.
27	“SMS201-995”.mp.
28	“SMS 201 995”.mp.
29	“SMS201 995”.mp.
30	“SMS 201995”.mp.
31	“SMS201995”.mp.
32	“SANDOSTATIN$”.mp
33	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	“LANREOTID$”.mp.
35	“BIM 23014”.mp.
36	“BIM23014”.mp.
37	“SOMATULIN$”.mp.
38	34 or 35 or 36 or 37
40	“VAPREOTIDE”.mp
41	“RC-160”.mp
42	“RC160”.mp
43	40 or 41 or 42
44	“somatostatin$”.mp.
45	“ANALOGUE$”.mp.
46	44 or 45
47	33 or 38 or 43 or 46
48	24 and 47
49	48 and 21

EMBASE 1980-2000 (on OVID)

1	Randomi#ed controlled trial$.mp.
2	Random allocation.mp
3	Double blind method.mp.
4	Single blind method.mp.
5	Clinical trial.mp.
6	Exp clinical trial/
7	(clin$ adj25 trial$).ti,ab.
8	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
9	Placebos/
10	Placebo$.ti,ab.
11	Research design/

12 Or/1-11
13 Animal.sh.
14 “animal”.mp.
15 13 or 14
16 “human”.mp.
17 15 not (15 and 16)
18 12 not 17
19 Acromegaly/ or “acromegaly”.mp.
20 “Acromegal$”.mp.
21 19 or 20
22 Octreotide/
23 “octreotid$”.mp.
24 “Sandostatin$”.mp.
25 “SMS 201-995”.mp.
26 “SMS201-995”.mp.
27 “SMS 201 995”.mp.
28 “SMS201 995”.mp.
29 “SMS 201995”.mp.
30 “SMS201995”.mp.
31 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 “Lanreotid$”.mp.
33 “BIM 23014”.mp.
34 “BIM23014”.mp.
35 “somatulin$”.mp.
36 32 or 33 or 34 or 35
37 “VAPREOTIDE”.mp.
38 “RC-160”.mp.
39 “RC160”.mp.
40 37 or 38 or 39
41 somatostatin/ or somatostatin analog/ or “somatostatin$.mp
42 “analogue$”.mp.
43 41 and 42
44 31 or 36 or 40 or 43
45 21 and 44
46 45 and 18

Cochrane Controlled Trials Register (Cochrane Library Issue 1, 2000)

1 Acromegaly
2 Somatostatin
3 Octreotide
4 Sandostatin
5 (SMS and 201-995)
6 SMS201-995
7 Lanreotide
8 Somatuline
9 (BIM and 23014)
10 BIM23014
11 Vapreotide
12 RC-160
13 RC160
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 1 and 14

PubMed (on National Library of Medicine)

1 Acromegaly
2 Octreotide
3 Lanreotide
4 Vapreotide
5 SMS 201-995
6 SMS201-995
7 BIM 23014
8 BIM23014
9 RC-160
10 RC160
11 Somatostatin analogue$
12 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13 #1 AND #12
14 #13 Limits: Publication Date from 1999 to 2000
15 #14 Limits: Publication Date from 1999 to 2000, Clinical Trial

Science Citation Index (on BIDS)

1 (Acromegaly) @TKA
2 (Octreotide) @TKA
3 (Lanreotide) @TKA
4 (Vapreotide) @TKA
5 (SMS 201-995) @TKA
6 (SMS201-995) @TKA
7 (BIM 23014) @TKA
8 (BIM23014) @TKA
9 (RC-160)@TKA
10 (RC160)@TKA
11 (Somatostatin analogue$) @TKA
12 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 (Random) @TKA
14 (Randomized) @TKA
15 (Trial) @TKA
16 (Blind) @TKA
17 13 or 14 or 15 or 16
18 1 AND 12
19 18 AND 17

B. Cost Effectiveness

MEDLINE 1966-2000 & EMBASE 1980-2000 (on OVID)

1 Exp cost-benefit analysis/ or exp economics, pharmaceutical/ or exp health care costs/ or "cost or economic evaluation or cost-effectiveness".mp
2 1 and 48 *(from MEDLINE search for clinical effectiveness) or* and 45 *(from EMBASE search for clinical effectiveness)*

NHS EED & DARE (Cochrane Library Issue 1, 2000), Bandolier (on line) & The Drugs and Therapeutics Bulletin (on line)

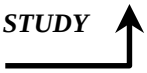
1 Acromegaly

Appendix 4 - Inclusion Criteria

A. Adjuvant Therapy

What is the effectiveness and cost effectiveness of somatostatin analogues versus conventional therapy in the treatment for patients with acromegaly where the disease is not controlled by surgery and/or radiotherapy?

Study Design:	Is the study an RCT **or** a non randomised trial with a concurrent parallel control group of a similar population	**Y**	**N**	**U**
Population:	Is the population patients with acromegaly?	**Y**	**N**	**U**
	Have the majority (>50%) of patients either undergone surgery to debulk / remove a tumour **or** have/are undergone/going radiotherapy?	**Y**	**N**	**U**
Intervention:	Is the intervention a somatostatin analogue *(Sandostatin/Octreotide/SMS 201-995/Somatuline/Lanreotide/ BIM 23014//Vapreotide/RC-160)* alone or in combination with other medical *(drug)* intervention(s)?	**Y**	**N**	**U**
Comparator:	Is the comparator a placbo **or** no treatment **or** another medical *(drug)* therapy *(dopamine agonist, GH receptor antagonist or other)* with or without somatostatin analogue	**Y**	**N**	**U**
Exclusion:	Is only one dose of the primary intervention given throughout the duration of the study **or** are the main outcomes measured after single dose(s) of the primary intervention?	**N**	**Y**	**U**

IF ALL ANSWERS ARE <u>IN</u> THIS COLUMN <u>INCLUDE</u> THE STUDY 

B. Primary Therapy

What is the effectiveness of somatostatin analogues versus conventional therapy as a primary treatment for acromegaly?

Study Design:	Is the study an RCT?	**Y**	**N**	**U**
Population:	Is the population patients with acromegaly?	**Y**	**N**	**U**
	Are the patients all previously untreated?	**Y**	**N**	**U**
Intervention:	Is the intervention a somatostatin analogue? *(eg. Sandostatin/Octreotide/SMS 201-995/Somatuline/Lanreotide/ BIM 23014/Vapreotide/RC-160)*	**Y**	**N**	**U**
Comparator:	Is the comparator any other primary treatment *(eg. surgery, radiotherapy, dopamine agonist, somatostatin analogue)* **or** placebo **or** no treatment?	**Y**	**N**	**U**

IF ALL ANSWERS ARE <u>YES</u> INCLUDE THE STUDY

C. Neo-Adjuvant Therapy

What is the effectiveness of somatostatin analogues as pre-surgical treatment for acromegaly?

Study Design:	Is the study an RCT?	**Y**	**N**	**U**
Population:	Is the population patients with acromegaly?	**Y**	**N**	**U**
	Are all the patients awaiting surgery to remove/debulk a tumour?	**Y**	**N**	**U**
Intervention:	Is the intervention a period of treatment with a somatostatin analogue *(Sandostatin/Octreotide/SMS 201-995/Somatuline / Lanreotide /BIM 23014/Vapreotide/RC-160)* followed by surgery to remove / debulk a tumour?	**Y**	**N**	**U**
Comparator:	Is the comparator any other pre-surgerical intervention *(radiotherapy, dopamine agonist, somatostatin analogue)* then surgery **or** placebo then surgery **or** surgery alone?	**Y**	**N**	**U**

IF ALL ANSWERS ARE <u>YES</u> INCLUDE THE STUDY

D. Analogue Comparison

What is the effectiveness of the different somatostatin analogues in the treatment of acromegaly?

Study Design:	Is the study an RCT?	**Y**	**N**	**U**
Population:	Is the population patients with acromegaly?	**Y**	**N**	**U**
Intervention:	Is the intervention a somatostatin analogue? *(Sandostatin/Octreotide/SMS 201-995/Somatuline/Lanreotide/ BIM 23014/Vapreotide/RC-160)*	**Y**	**N**	**U**
Comparator:	Is the comparator a different somatostatin analogue *(Sandostatin/Octreotide/SMS 201-995/Somatuline/Lanreotide/BIM 23014/Vapreotide/RC-160) or a different form (i.e. microencapsulated) of the same somatostatin analogue*?	**Y**	**N**	**U**
Exclusion:	Is this solely a dose range study on the same analogue preparation *(analogue preparations are Octreotide sc, LAR, Lanreotide LA etc.)* administered by the same regime *(regimes are sc injection, im injection, continuous infusion, nasal spray etc.)?*	**N**	**Y**	**U**
Exclusion:	Is only one dose of the intervention or comparator given throughout the duration of the study **or** are the main outcomes measured after single dose(s) of the intervention or comparator?	**N**	**Y**	**U**

IF ALL ANSWERS ARE <u>IN</u> THIS COLUMN <u>INCLUDE</u> THE STUDY

Appendix 5 - Quality Assessment

Quality Assessment
Somatostatin Analogues in the Treatment of Acromegaly

Question: **Primary Treatment** **Pre-Surgery Treatment** **Analogue Comparison** **Adjuvant Therapy**
Reviewers Initials: Authors: Pub Year:

A		Randomisation			
	1	Was the trial described as randomised		N	Y
	2	Was allocation truly random? *(random numbers❑ coin toss❑ Other)*		A	
		Was allocation quasi random? *(patient number❑ DOB❑Other)*		B	
		Was allocation systematic? *(alternate ❑Other)*		C	
		Was method of randomisation not stated / unclear		D	
B		Allocation concealment			
	1	Was concealment adequate?(*Central allocation at trials office ❑pharmacy ❑or other method where trialist could not be aware of treatment)*		A	
		Was concealment inadequate? *Alternate (day of week❑admission ward❑by patient) based on DOB❑or info already known to trialist)*		B	
		Was concealment unclear?		C	
C		Blinding			
	1	Was the trial described as double blind		N	Y
	2	Was treatment allocation masked from participants *(stated❑or identical placebo❑)*	U	N	Y
	3	Was treatment allocation masked from investigators	U	N	Y
	4	Was treatment allocation masked from outcome assessor	U	N	Y
D		Completeness			
	1	Were the number of withdrawals in each group stated	U	N	Y
	2	Was an intention to treat analysis performed	U	N	Y
	3	What were the follow up rates (%) in each group of the trial for each of the main outcomes *(use unclear or not stated as appropriate)*			

Group	Outcome 1	Outcome 2	Outcome 3	

4	Are there substantial differences in completeness between the groups	U	N	Y

Jadad Scale - Scoring

Criteria	**Circle if criterion satisfied**
Does A1 = YES	+1
Does C1 = YES	+1
Does D1 = YES	+1
Does A2 = A **&** B1 = A	+1
Does A1 = YES **&** A2 = B or C **or** B1 = B	-1
Does C2 = YES **&** C4 = YES	+1
Does C1 = YES **&** C2 = NO **or** C4 = NO	-1
Total Score (0 – 5)	

Comments:

Appendix 6 - Data Extraction Proforma

SOMATOSTATIN ANALOGUES IN THE TREATMENT OF ACROMEGALY

Question: **Primary Treatment** **Neo Adjuvant Treatment** **Analogue Comparison** **Adjuvant Therapy**

Reviewers Initials: Authors: Pub Year:

STUDY DESIGN

Trial Name (if any) :

Type of Trial: Randomised Y N U
Parallel Y N U
Crossover Y N U
Blinded Y N U

Who was blinded: Patients❑ Investigator❑ Outcome Assessor❑ (*Outcomes blinded if not all:* *)*
Unclear❑

Number of Centres: Location(s):

POPULATION

Patient Inclusion/Exclusion Criteria:

Number Approached: Excluded: Included:

Maximum Length of Followed Up

POPULATION CHARACTERISTICS

	Intervention Group			
	A	**B**	**C**	**D**
Intervention				
Number				
Mean Age (±SD)				
Gender Mix				
Ethnic Mix				
Mean Duration of Acromegaly (±SD) (from Diagnosis or Symptoms or Unclear)				
Previous Treatments				

Were the Groups Comparable at Entry:

INTERVENTION

	Intervention Group			
	A	**B**	**C**	**D**
Wash Out Period before Commencing Trial				
Intervention/Drug				
Dose/Frequency				
Method of Administration (Eg sc, im)				
Time of Administration				
Duration of Treatment				
Wash Out Period before X-over				

OUTCOMES MEASURED

Outcome	**Test Used/Assay Method**	**When Measured**	**Where Measure**	**By Whom**	**Other** Eg Cut Off Level for Classifying Cure, Fasting

STATISTICAL METHODS EMPLOYED BY TRIALISTS

OUTCOMES

After GH & IGF-1, complete the blank rows for other outcomes as they appear in the text.

	Intervention Group			
	A	**B**	**C**	**D**
Intervention/Drug /Dose				
GH *Note where possible:* **Baseline mean (SD&n)** **End Point Means (SD&n)** **Other Milestones Mean Change (SD/SE)** **P values** **% Reaching < Cure Level** **n not measured**				
IGF-1 **(Somatomedin C)** *Note where possible:* **Baseline mean (SD&n)** **End Point Means (SD&n)** **Other Milestones Mean Change (SD/SE)** **P values** **% Reaching < Cure Rate** **n not measured**				
Other Outcomes				

ADVERSE EVENTS

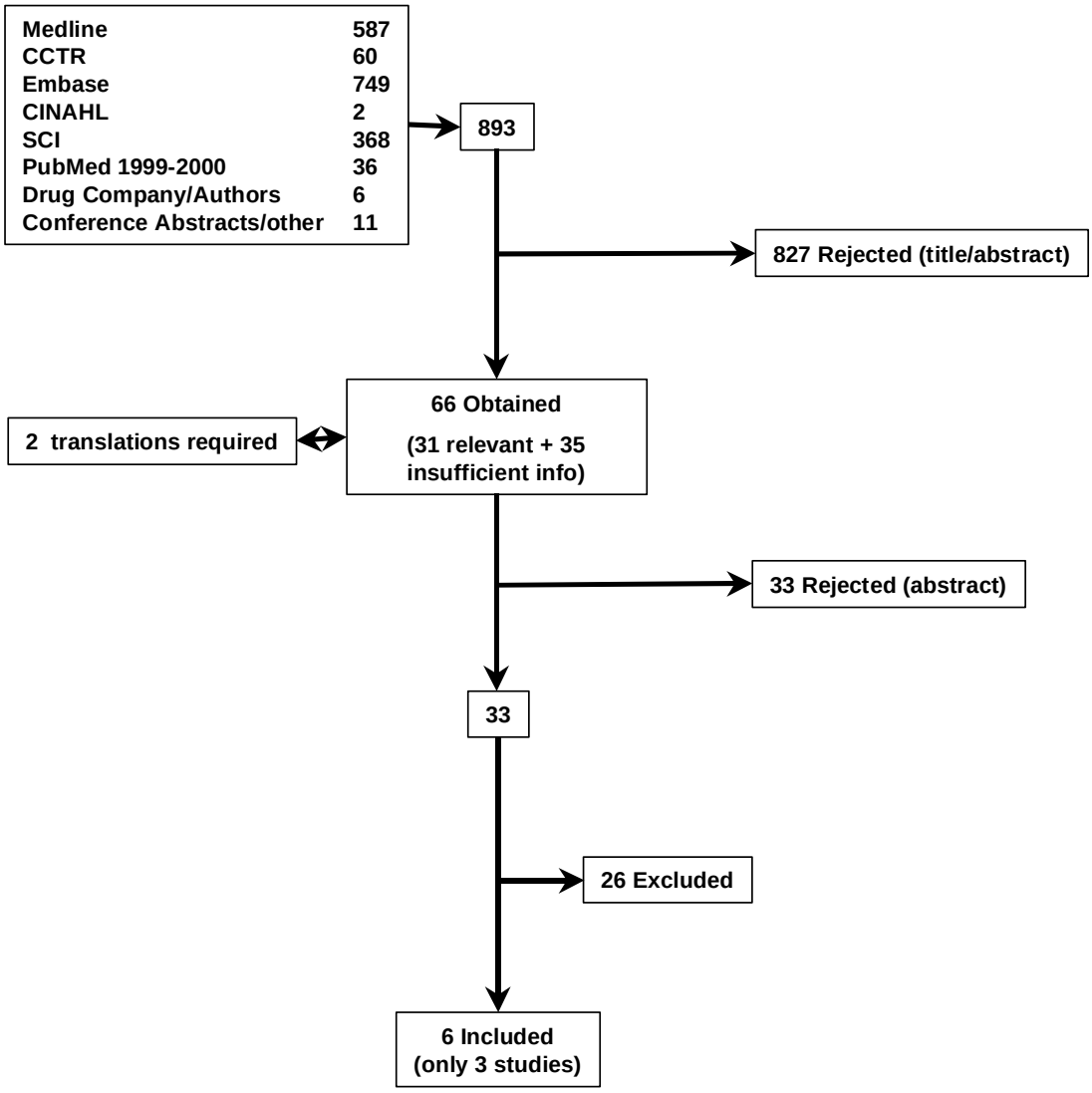
	Intervention Group			
	A	**B**	**C**	**D**
Intervention/Drug/Dose				
Injection Site Pain				
Gall Bladder: Billiary sludge				
Gallstones (symptomatic & asymptomatic)				
Gastrointesinal: Nausea				
Diarrhoea				
Cramps				
Loose/Softened Stools				
Flatulence				
Constipation				

DROP OUTS/LOSSES TO FOLLOW UP
(For each outcome note numbers (%) and reasons)

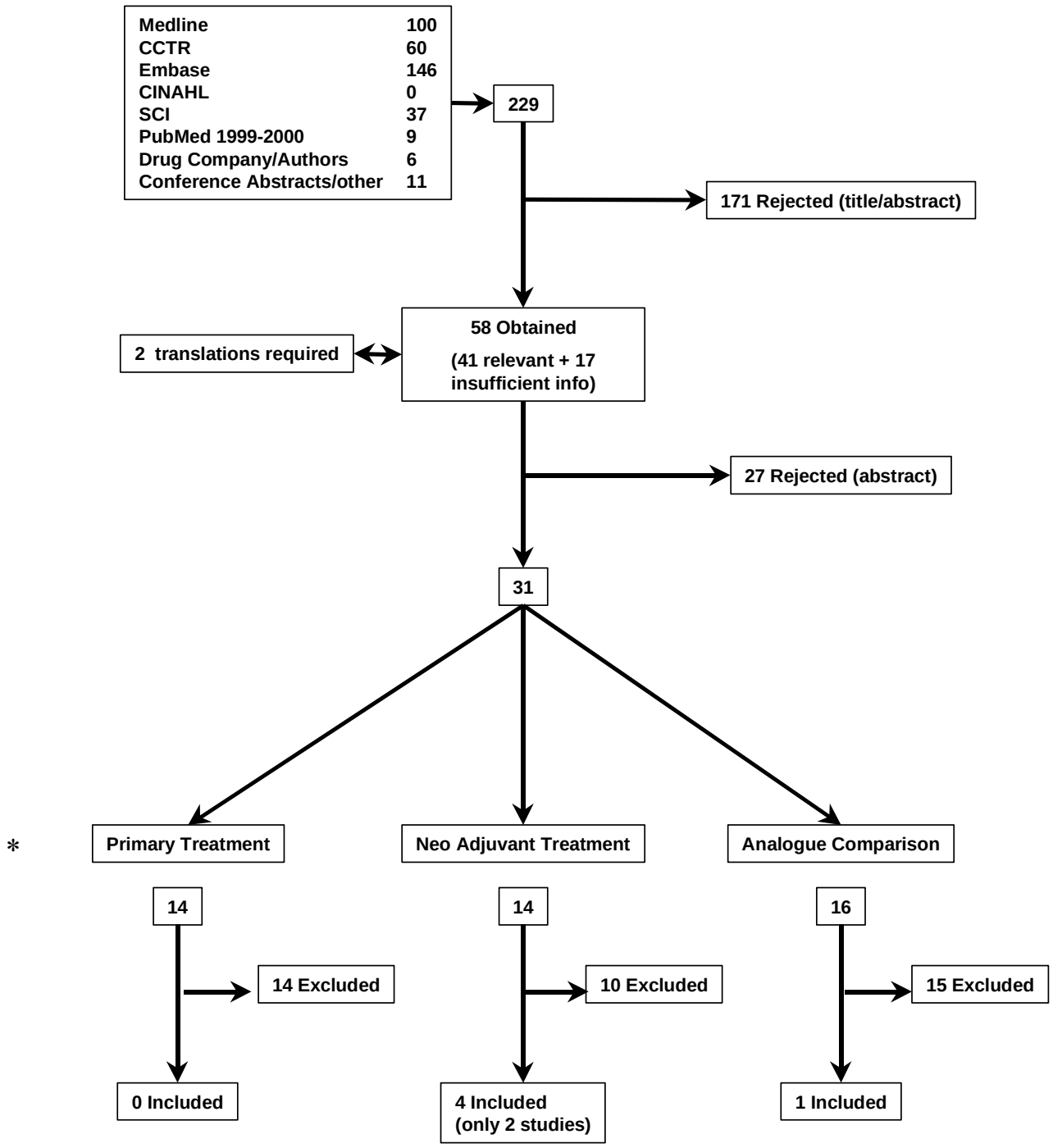
OTHER

Appendix 7 - Search Results

A. Adjuvant Treatment



B. Primary Treatment, Neo-Adjuvant Treatment and Analogue Comparison



** NB. Some trials appeared relevant to more than one review question*

Appendix 8 - Included and Excluded Studies

A. Adjuvant Treatment

Included Studies

Ezzat and Colleagues

- Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, *et al*. Octreotide treatment of acromegaly. *Ann Intern Med* 1992;117:711-718.
- Newman C, Melmed S, Torigian AJD, Duhaney M, Snyder P, Young W, *et al*. Octreotide as primary therapy for acromegaly. *J Clin Endocrinol Metab* 1998;83:3034-3040.

Fredstorp and Colleagues

- Fredstorp L, Harris A, Haas G, Werner S. Short term treatment of acromegaly with the somatostatin analog octreotide: the first double-blind randomized placebo-controlled study of its effects. *J Clin Endocrinol Metab 1990;71:1189-1194.*
- Fredstorp L, Werner S. Growth hormone and insulin-like growth factor-1 in blood and urine as response markers during treatment of acromegaly with octreotide: a double-blind placebo-controlled study. *J Endocrinol Invest* 1993;16:253-258.
- Fredstorp L, Werner S, Bang P, Hall K. Inverse correlation between insulin-like growth factor binding protein-1 and insulin in patients with acromegaly during treatment with the somatostatin analogue octreotide. *Clin Endocrinol* 1994;41:495-501.

Halse and Colleagues

- Halse J, Harris AG, Kvistborg A, Kjartansson O, Hanssen E, Smiseth O, *et al*. A randomized study of SMS 201-995 versus bromocriptine treatment in acromegaly:clinical and biochemical effects. *J Clin Endocrinol Metab* 1990;70:1254-1261.

Excluded Studies

Study/Article	Inclusion Criteria Adhered To					
	Is the study an RCT or a non randomised trial with concurrent control group of similar population?	Is the population patients with acromegaly?	Have the majority (>50%) of patients either undergone surgery and or radiotherapy?	Is the intervention a somatostatin analogue?	Is the comparator a placebo or no treatment or another medical therapy with/without somatostatin analogue?	Is more than one dose of the intervention or comparator given throughout the duration of the study or are the main outcomes measured after more than a single dose of the intervention or comparator?
Sandler LM, Burrin LM, Joplin GF, Bloom SR. Effect of high dose somatostatin analogue on growth hormone concentrations in acromegaly. *BMJ* 1988;296:751-52.	N	Y	?	Y	N	Y
Sicolo N, Martini C, Ferla S, Roggenkamp J, Vettor R, De Palo C, *et al*. [Analgesic effect of Sandostatin (SMS 201-995) in acromegaly headache]. [Italian]. *Minerva Endocrinol* 1990;15:37-42.	N	Y	?	Y	Y	N
Gasinska T, Nowak S. [Response of growth hormone to sandostatin and bromocriptine and prognostic value of prolactin levels in serum and thyroliberin test in patients with active acromegaly]. [Polish]. *Endokrynologia Polska* 1993;44:455-65.	N	Y	Y	Y	Y	N
Hansen TA, Gram J, Bjerret P, Hagen C, Bollerslev J. Body composition in active acromegaly during treatment with octreotide: A double-blind, placebo-controlled cross-over study. *Clin Endocrinol* 1994;41:323-9.	Y	Y	N	Y	Y	Y
Van Liessum PA, Hopman WP, Pieters GF, Smals AG, Tangerman A, Jansen JB, *et al*. Postprandial exocrine pancreatic function during long-term treatment with the somatostatin analogue SMS 201-995 in acromegalic patients. *Euro J Clin Invest* 1990;20:348-53.	N	Y	?	Y	Y	N
Riedel M, Gunther T, von zur M, Brabant G. The pulsatile GH secretion in acromegaly: hypothalamic or pituitary origin? *Clin Endocrinol* 1992;37:233-9.	Y	Y	Y	Y	N	Y
Chanson P, Timsit J, Benoit O, Augendre B, Moulonguet M, Guillausseau, PG, *et al*. Rapid improvement in sleep apnoea of acromegaly after short-term treatment with somatostatin analogue SMS 201-995. *Lancet* 1986;1(8492):1270-1.	N	N	Y	Y	N	Y
Van Liessum PA, Hopman WP, Pieters GF, Jansen JB, Smals AG, Rosenbusch, *et al*. Postprandial gallbladder motility during long term treatment with the long-acting somatostatin analog SMS 201-995 in acromegaly. *J Clin Endocrinol Metab* 1989;69:557-62.	N	Y	?	Y	Y	N
Hussaini SH, Pereira SP, Kennedy C, et al. Meal-stimulated gallbladder (GB) emptying in acromegaly: the effect of octreotide (OT) treatment. [Abstract] *Gut* 1994;35:S57	Y	Y	?	Y	Y	N
Minniti G, Jaffrain-Rea ML, Baldelli R, Ferretti E, Caracciolo B, Bultrini A, *et al*. Acute effects of octreotide, cabergoline and a combination of both drugs on GH secretion in acromegalic patients. *Clin Ter* 1997;148:601-7.	N	Y	N	Y	Y	Y
Andersen M, Hansen TB, Bollerslev J, Bjerre P, Schroder HD, Hagen C. Effect of 4 weeks of octreotide treatment on prolactin, thyroid stimulating hormone and thyroid hormones in acromegalic patients. A double blind placebo-controlled cross-over study. *J Endocrinol Invest* 1995;18:840-6.	Y	Y	N	Y	Y	N

Yang IM, Woo JT, Kim SW, Kim JW, Kim YS, Choi YK. Characteristics of acromegalic patients with a good response to octreotide, a somatostatin analogue. *Clin Endocrinol* 1995;42:295-301.	N	Y	N	Y	N	N
Lombardi G, Colao A, Ferone D, Sarnacchiaro F, Marzullo P, Di Sarno A, *et al*. CV 205-502 treatment in therapy-resistant acromegalic patients. *Eur J Endocrinol* 1995;132:559-64.	Y	Y	Y	Y	Y	N
George SR, Hegele RA, Burrow GN. The somatostatin analogue SMS 201-995 in acromegaly: prolonged, preferential suppression of growth hormone but not pancreatic hormones. *Clin Invest Med* 1987;10:309-15.	Y	Y	?	Y	Y	N
Anderson JV, Catnach S, Lowe DG, Fairclough PD, Besser GM, Wass JA. Prevalence of gastritis in patients with acromegaly: untreated and during treatment with octreotide. *Clin Endocrinol* 1992;37:227-32.	N	Y	?	Y	N	Y
Atkinson AB, McKnight JA, McCance DR, Bell PM. Somatostatin analogue (SMS 201-995) in resistant acromegaly: a preliminary report. *Horm Res* 1990;33 Suppl 1:7-11.	N	Y	Y	Y	Y	Y
Lamberts SW, Zweens M, Verschoor L, del Pozo E. A comparison among the growth hormone-lowering effects in acromegaly of the somatostatin analog SMS 201-995, bromocriptine, and the combination of both drugs. *J Clin Endocrinol Metab* 1986;63:16-9.	Y	Y	N	Y	Y	N
Van Liessum PA, Pieters GF, Smals AG, Hermus AR, Benraad TJ, Kloppenborg, PW. Single-dose response study of the somatostatin analogue octreotide in acromegaly. *Acta Endocrinol* 1989;121:714-20.	Y	Y	N	Y	Y	N
McKnight JA, McCance DR, Crothers JG, Atkinson AB. Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly. *BMJ* 1989;299:604-5.	N	Y	Y	Y	N	Y
Oppizzi G, Petroncini MM, Dallabonzana D, Cozzi R, Verde G, Chiodini PG, *et al*. Relationship between somatomedin-C and growth hormone levels in acromegaly: basal and dynamic evaluation. J Clin Endocrinol Metab 1986;63:1348-53.	N	Y	?	Y	Y	Y
Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, *et al*. Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996;38:775-83.	Y/N*	Y/Y*	?/?*	Y/Y*	Y/N*	N/Y*
Schmidt K, Althoff PH, Harris AG, Prestele H, Schumm-Draeger PM, Usadel, KH. Analgesic effect of the somatostatin analogue octreotide in two acromegalic patients: a double-blind study with long-term follow-up. *Pain* 1993;53:223-7.	?	Y	?	Y	Y	N
Chiodini PG, Cozzi R, Dallabonzana D, Oppizzi G, Verde G, Petroncini M, *et al*. Medical treatment of acromegaly with SMS 201-995, a somatostatin analog: a comparison with bromocriptine. *J Clin Endocrinol Metabol* 1987;64:447-53.	N/N*	Y/Y*	Y/N*	Y/Y*	Y/Y*	Y/N*
Barreca A, Cariola G, Ponzani P, Arvigo M, Foppiani L, Giordano G, *et al*. Effect of octreotide on circulating IGF-I chromatographic profile: evidence for an inhibitory action on the formation of the 150-kDa ternary complex. *Clin Endocrinol* 1995;42:161-7.	?	Y	?	Y	Y	Y
de Herder WW, Uitterlinden P, van der Lely AJ, Hofland LJ, Lamberts SW. Octreotide, but not bromocriptine, increases circulating insulin-like growth factor binding protein 1 levels in acromegaly. *Eur J Endocrinol* 1995;133:195-9.	N	Y	N	Y	Y	N
Wilson LS, Shin JL, Essat S. Cost analysis of the different therapeutic options in the management of acromegaly. Conference abstract. Endo 99 - 81st Annual Meeting of the Endocrinology Society 1999. Accessed Online::www.abstracts-on-line.com/abstracts/endo-society [accessed 9/5/00]	N	Y	?	Y	Y	Y
Wagenaar AH, Harris AG, van der Lely AJ, Lamberts SW. Dynamics of the acute effects of octreotide, bromocriptine and both drugs in combination on growth hormone secretion in acromegaly. *Acta Endocrinol* 1991;125:637-42.	N	Y	N	Y	Y	N

Y-Yes. N-No. ?-Insufficient information available. *Two-phase studies.

B. Neo-Adjuvant Treatment

Included Studies

Ezzat and Colleagues

- Ezzat S, Horvath E, Harris AG, Kovacs K. Morphological effects of octreotide on growth hormone-producing pituitary adenomas. *J Clin Endocrinol Metab* 1994;79:113-8
- Ezzat S, Kontogerorgos G, Redelmeier DA, Horvath E, Harris AG, Kovacs K. In vivo responsiveness of morphological variants of growth hormone-producing pituitary adenomas to octreotide. *Eur J Endocrinol* 1995;133:686-90
- Thapar K, Kovacs K, Stefaneanu L, Scheithauer BN, Horvath E, Lloyd RV *et al*. Antiproliferative effect of the somatostatin analogue octreotide on growth hormone-producing pituitary tumors: results of a mulitcenter randomized trial. *Mayo Clin Proc* 1997;72:893-900

Zgliczynski

- Zgliczynski S. Un pré-traitement par le lanréotide LP améliore les résultats de la chirurgie chez des patients atteints de tumeurs hypophysaires avec récepteurs à la somatostatine. *Ann Endocrinol (Paris) 1998;59:34-35.*

Excluded Studies

Study/Article	Inclusion Criteria Adhered To				
	Is the study an RCT?	Is the population patients with acromegaly?	Are the patients awaiting surgery to remove/debaulk a tumour?	Is the intervention treatment with somatostatin analogue followed by surgery?	Is the comparator any other presurgical intervention or placebo or no treatment and then surgery?
Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, *et al*. Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann Intern Med* 1992;117:711-8.	Y	Y	?	N	N
Stevenaert A, Beckers A. Presurgical Octreotide: treatment in acromegaly. *Metabolism* 1996;45(8 Suppl 1):72-4.	N	Y	Y	Y	Y
Halse J, Harris AG, Kvistborg A, Kjartansson O, Hanssen E, Smiseth O, *et al*. A randomized study of SMS 201-995 versus bromocriptinetreatment in acromegaly:clinical and biochemical effects. *J Clin Endocrinol Metab* 1990;70:1254-1261.	Y	Y	?	N	N
Kristof RA, Stoffel-Wagner B, Klingmuller D, Schramm J. Does octreotide treatment improve the surgical results of macro-adenomas in acromegaly? A randomized study. *Acta Neurochir* 1999;141:399-405.	N	Y	Y	Y	Y
Tsukamoto N, Nagaya T, Kuwayama A, Takano K, Shizume K, Sugita K, *et al.* Octreotide treatment results in the inhibition of GH gene	N	Y	Y	Y	Y

expression in the adenoma of the patients with acromegaly. *Endocr J* 1994;41:437-44.					
Colao A, Ferone D, Cappabianca P, De Caro MLDB, Marzullo P, Monticelli, *et al*. Effect of octreotide pretreatment on surgical outcome in acromegaly. *J Clin Endocrinol Metab* 1997;82:3308-14.	N	Y	Y	Y	Y
Wasko R, Ruchala M, Sawicka J, Kotwicka M, Liebert W, Sowinski J. Short-term pre-surgical treatment with somatostatin analogues, octreotide and lanreotide, in acromegaly. *J Endocrinoll Invest* 2000;23:12-8.	N	Y	Y	Y	Y
Plockinger U, Reichel M, Fett U, Saeger W, Quabbe HJ. Preoperative octreotide treatment of growth hormone-secreting and clinically nonfunctioning pituitary macroadenomas: effect on tumor volume and lack of correlation with immunohistochemistry and somatostatin receptor scintigraphy. *J Clin Endocrinol Metab* 1994;79:1416-23.	N	Y	Y	Y	N
Frysak Z, Machac J. Somatostatin analog in the preoperative treatment of acromegaly. *Cesk Slov Neur Neurochir* 1999;62:242-3.	N	Y	Y	Y	N
Stevenaert A, Beckers A. Presurgical octreotide treatment in acromegaly. *Acta Endocrinol* 1993;129 Suppl 1:18-20.	N	Y	Y	Y	Y

Y-Yes. N-No. ?-Insufficient information available

C. Primary Treatment

Included Studies

None

Excluded Studies

Study/Article	Inclusion Criteria Adhered To				
	Is the study an RCT?	Is the population patients with acromegaly?	Are the patients all previously untreated?	Is the intervention a somatostatin analogue?	Is the comparator a primary treatment or placebo or no treatment?
Andersen M, Hansen TB, Bollerslev J, Bjerre P, Schroder HD, Hagen C. Effect of 4 weeks of octreotide treatment on prolactin, thyroid stimulating hormone and thyroid hormones in acromegalic patients. A double blind placebo-controlled cross-over study. *J Endocrinol Invest* 1995;18:840-6.	Y	Y	N*	Y	Y
Chiodini PG, Cozzi R, Dallabonzana D, Oppizzi G, Verde, Petroncini M, *et al*. Medical treatment of acromegaly with SMS 201-995, a somatostatin analog: a comparison with bromocriptine. *J Clin Endocrinol Metab* 1987;64:447-53.	Y	Y	N*	Y	Y
Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, *et al*. Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann Intern Med* 1992;117:711-8.	Y	Y	N*	Y	Y
Fredstorp L, Harris A, Haas G, Werner S. Short term treatment of acromegaly with the somatostatin analog octreotide: the first double-blind randomized placebo-controlled study on its effects. *J Clin Endocrinol Metab* 1990;71:1189-94.	Y	Y	N*	Y	Y
Fredstorp L, Werner S, Bang P, Hall K. Inverse correlation between insulin-like growth factor binding protein-1 and insulin in patients with acromegaly during treatment with the somatostatin analogue octreotide. *Clin Endocrinol* 1994;41:495-501.	?	Y	N	Y	Y
Halse J, Harris AG, Kvistborg A, Kjartansson O, Hanssen E, Smiseth O, *et al*. A randomized study of SMS 201-995 versus bromocriptinetreatment in acromegaly:clinical and biochemical effects. *J Clin Endocrinol Metab* 1990;70:1254-1261..	Y	Y	N*	Y	Y
Hansen TB, Gram J, Bjerre P, Hagen C, Bollerslev J. Body composition in active acromegaly during treatment with octreotide: a double-blind, placebo-controlled cross-over study. *Clin Endocrinol* 1994;41:323-9.	Y	Y	N*	Y	Y
Hussaini SH, Pereira SP, Kennedy C, et al. Meal-stimulated gallbladder (GB) emptying in acromegaly:the effect of octreotide (OT) treatment. *Gut* 1994;35:S57	Y	Y	?*	Y	Y
Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, *et al*. Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996;38:775-83.	Y	Y	?*	Y	Y

Lamberts SW, Verleun T, Hofland L, del Pozo E. A comparison between the effects of SMS 201-995, bromocriptine and a combination of both drugs on hormone release by the cultured pituitary tumour cells of acromegalic patients. *Clin Endocrinol* 1987;27:11-23.	N	Y	Y	Y	Y
Minniti G, Jaffrain-Rea ML, Baldelli R, Ferretti E, Caracciolo B, Bultrini A, ***et al.*** Acute effects of octreotide, cabergoline and a combination of both drugs on GH secretion in acromegalic patients. *Clin Ter* 1997;148:601-7.	N	Y	N	Y	Y
Newman CB, Melmed S, George A, Torigian D, Duhaney M, Snyder P, *et al*. Octreotide as primary therapy for acromegaly [see comments]. *J Clin Endocrinol Metab* 1998;83:3034-40.	Y	Y	N	Y	Y
Schmidt K, Althoff PH, Harris AG, Prestele H, Schumm-Draeger PM, Usadel, KH. Analgesic effect of the somatostatin analogue octreotide in two acromegalic patients: a double-blind study with long-term follow-up. *Pain* 1993;53:223-7.	?	Y	?*	Y	Y
Van Liessum PA, Hopman WP, Pieters GF, Jansen JB, Smals AG, Rosenbusch, ***et al.*** Postprandial gallbladder motility during long term treatment with the long-acting somatostatin analog SMS 201-995 in acromegaly. *J Clin Endocrinol Metab* 1989;69:557-62.	?	Y	N*	Y	Y

Y-Yes. N-No. ?-Insufficient information available

* These studies were excluded solely on the basis of the population not being total composed of untreated patients. None of the patients in these studies were stratified at randomisation for previous and no previous treatment.

D. Analogue Comparison

Included Studies

Chanson and colleagues

- Chanson P, Boerlin V, Ajzenberg C, Bachelot Y, Benito P, Bringer J, *et al*. Comparison of octreotide acetate LAR and lanreotide SR in patients with acromegaly. *Clin Endocrinol* 2000;53:577-86

Excluded Studies

Study/Article	Inclusion Criteria Adhered To					
	Is the study an RCT?	Is the population patients with acromegaly?	Is the intervention a somatostatin analogue?	Is the comparator a somatostatin analogue?	Is this not a dose range study on the same analogue preparation administered by the same regime?	Is more than one dose of the intervention or comparator given throughout the duration of the study or are the main outcomes measured after more than a single dose of the intervention or comparator?
Pedroncelli A, Lancranjan I, Montini M, et al. The effects of different long-acting somatostatin analogues in the management of acromegaly. [Abstract] Endo '99 - 81st Annual Meeting of The Endocrinology Society 1999. Accessed On Line: www.abstracts-on-line.com/abstracts/endo-society [accessed 9/5/00]	N	Y	Y	Y	Y	Y
Turner HE, Vadivale A, Wass JA. Lanreotide and Octreotide LAR for treatment of acromegaly. [Abstract] Endo '99 - 81st Annual Meeting of The Endocrinology Society 1999 Accessed On Line: www.abstracts-on-line.com/abstracts/endo-society [accessed 9/5/00]	N	Y	Y	Y	Y	Y
Colao A, Marzullo P, Ferone D, Marino V, Pivonello R, Di Somma C, *et al*. Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly. *J Endocrinol Invest* 1999;22:40-7.	N	Y	Y	Y	Y	Y
Ezzat S, Snyder PJ, Young WF, Boyajy LD, Newman C, Klibanski A, *et al*. Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann Intern Med* 1992;117:711-8.	Y/Y*	Y/Y*	Y/Y*	Y/N*	N/Y*	Y/Y*
Hunter SJ, Shaw JA, Lee KO, Wood PJ, Atkinson AB, Bevan JS. Comparison of monthly intramuscular injections of Sandostatin LAR with multiple subcutaneous injections of octreotide in the treatment of acromegaly; effects on growth hormone and other markers of growth hormone secretion. *Clin Endocrinol* 1999;50:245-51.	N	Y	Y	Y	Y	Y
Weeke J, Christensen SE, Orskov H, Kaal A, Pedersen MM, Illum P, *et al*. A randomized comparison of intranasal and injectable octreotide administration in patients with acromegaly. *J Clin Endocrinol Metab* 1992;75:163-9.	Y	Y	Y	Y	Y	N

Timsit J, Chanson P, Larger E, Duet M, Mosse A, Guillausseau PJ, *et al*. The effect of subcutaneous infusion versus subcutaneous injections of a somatostatin analogue (SMS 201-995) on the diurnal GH profile in acromegaly. *Acta Endocrinol* 1987;116:108-12.	N	Y	Y	Y	Y	Y
Morange I, De Boisvilliers F, Chanson P, Lucas B, Dewailly D, Catus F, *et al*. Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. J Clin Endocrinol Metab 1994;79:145-51.	N	Y	Y	Y	Y	Y
Caron P, Morange-Ramos I, Cogne M, Jaquet P. Three year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide]. *J Clinical Endocrinol Metab* 1997;82:18-22.	N	Y	Y	Y	Y	Y
Caron P, Cogne M, Gusthiot-Joudet B, Wakim S, Catus F, Bayard F. Intramuscular injections of slow-release lanreotide (BIM 23014) in acromegalic patients previously treated with continuous subcutaneous infusion of octreotide (SMS 201-995). *Eur J Endocrinol* 1995;132:320-5.	N	Y	Y	Y	Y	Y
Turner HE, Vadivale A, Keenan J, Wass JAH. A comparison of lanreotide and octreotide LAR for treatment of acromegaly. *Clin Endocrinol* 1999;51:275-80.	N	Y	Y	Y	Y	Y
Cozzi R, Dallabonzana D, Attanasio R, Barausse M, Oppizzi G. A comparison between octreotide-LAR and lanreotide-SR in the chronic treatment of acromegaly. *Eur J Endocrinol* 1999;141:267-71.	N	Y	Y	Y	Y	Y
Reidel M, Günther T, von zur Mühlen A, Brabant G. The pulsatile GH secretion in acromegaly: hypothalmic or pituitary origin? *Clin Endocrinol* 1992;37:233-39	Y	Y	Y	N	Y	Y
Harris AG, Weeke J, Christensen SE, Kaal A, Illum P, Orskov H. Preliminary results with Sandostatin nasal powder in acromegalic patients. *Metabolism* 1992;41(9 Suppl 2):72-5.	Y	Y	Y	Y	Y	N
Christensen SE, Weeke J, Orskov H, Kaal A, Lund E, Jorgensen J, *et al*. Long-term efficacy and tolerability of octreotide treatment in acromegaly. *Metabolism* 1992;41(9 Suppl 2):44-50.	N	Y	Y	Y	Y	Y

Y-Yes. N-No. * Two phase study

Appendix 9 - Characteristics, Quality and Outcomes of Included Trials

A. Adjuvant Treatment

Study Characteristics

Study / Reference	Type of Study / Location	Population					Intervention	Comparator	Length of follow up	Major Outcomes	Comments
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Other					
Halse and Colleagues[36]	Randomised parallel controlled open trial Norway	Symptoms/signs of active acromegaly & fasting GH >2.0 µg/l & GH level remaining elevated during OGTT	N/A (However no patients had pituitary surgery in the preceding 6 months, or radiotherapy in preceding 2 years or hypersecretion of a pituitary hormone other than GH)	26	SMS 201 995 / Bromo-criptine Surg 92 / 62 Brom 31 / 8 Rad 31 / 38 None 8 / 31	*Mean Age*: 49.2(I) 47.8 (C) Sex:10M:16F *Duration of Acromegaly*: Mean 6.5(I) 5.2 (C) yrs Bromocriptine treatment discontinued 30 days prior to study	*Drug:* SMS 201-995 (octreotide sc) *Dose:* Stepwise increase from 150µg/day in week 1 to 600µg/day in week 4-8. *Regime:* Sc injection 3x/day N=13	*Drug:* Bromocriptine *Dose:* Stepwise increase from 1.25mg.day in week 0.5 to 22.5mg/day in week 4-8. *Regime:* Oral 3x per day N=13	8 weeks treatment + 2 weeks follow up	Serum GH Serum IGF-1 Tolerance Side effects Signs and symptoms Biochemistry Tumour size	
Ezzat and Colleagues[31,32]	Mulit-centre Randomised double blind placebo controlled parallel trial 14 university affiliated medical centres Location: N/A	Acromegalics with Serum GH>2µg/l throughout a two hour OGTT	Patients having undergone radiotherapy in preceding 12 months, or bromocriptine treatment in previous month or octreotide at any time. Ectopic GHRH hypersecretion.patients with existing cholelithiasis excluded post randomisation(N=1)	116	Octre otide / Placebo Surg 64 / 76 Brom 46 / 59 Rad 39 / 33	*Mean Age*: 47(I) 45 (C) Sex: Unknown but I & C Matched *Duration of Acromegaly*: Unknown but I and C matched Bromocriptine treatment discontinued 1 month prior to study	*Drug:* Octreotide sc *Dose:*50µg/8 hrs in week 1 and 100µg/8hr in weeks 2-4 *Regime:* sc injection N=60	*Drug:* Placebo (not stated *Dose:*N/A *Regime*: Implied that same as for intervention N=55	4 weeks treatment + 4 weeks follow up	Serum GH Plasma IGF-1 Other hormone levels	Two-phase trial. First phase as outlined here, second phase a randomised dose range study and not reported here. Paper by Newman only reports on outcomes of this second phase.
Fredstorp and Colleagues[33-35]	Randomised double blind placebo controlled parallel trial Location: N/A	Symptoms/signs of active acromegaly & elevated GH levels & GH levels >2µg/l during an OGTT	No history of liver/kidney disease or MI within previous 6 months	20	Octre otide / Placebo Surg 80 / 50 Brom 30 / 0 Rad 60 / 40 None 20 / 50	*Mean Age*: 49.1(I) 54.0 (C) *Sex:M9:F11* *Duration of Acromegaly*: Unknown Bromocriptine or other dopamine agonist treatment discontinued 1 month prior to study	*Drug:* Octreotide sc *Dose:*50µg/8hrs day 1-2, 100µg/8hr day 3-4, 150µg/8hr day 5-6, 200µg/8hr day 7-14 *Regime:* sc injection N=10	*Drug:* Placebo (saline) *Dose:* corresponding volumes containing the same excipient as the treatment given at the same time *Regime: sc* injection N=10	14 days treatment + 6 days follow up	Plasma GH Serum IGF-1 Other hormone levels Haematology Signs and symptoms Adverse effects.	Single trial with different outcomes reported in each of three publications.

Brom: Bromocriptine. Rad: Radiotherapy. Surg: Surgery.

Quality

Study/ Reference	Type of Study/blinding	No. Patients	Allocation Concealment	Similarity between groups at baseline	Withdrawals stated	ITT	Follow up rates for major outcomes	Jadad Score	Comments
Halse and Colleagues[36]	Randomised, parallel open trial	26	Random numbers, concealment unclear	Yes	Yes	No	>80%	2	Well-reported study with fairly comprehensive range of outcome measures. Incomplete statistical analysis
Ezzat and Colleagues[31,32]	Mulit-centre Randomised double blind placebo controlled parallel trial	116	Randomisation method and concealment unclear,	Yes	Yes	Yes	GH/IGF-1: >89% 6 losses to follow up in each group.	3	Stated as being double blind but not sure who is blinded. Needs very detailed read to determine which group loss to follow up come from. Incomplete statistical analysis
Fredstorp and Colleagues[33-35]	Randomised double blind placebo controlled parallel trial	20	Randomisation method and concealment unclear	(Yes) *Some variation in previous treatments*	Yes	Yes	GH/IGF-1 100% Same rate for most outcomes	3	

Outcomes

Study	Mean Serum GH + sem (µg/l)											Mean IGF-1 + sem (U/ml)											Patient Status
	Somatostatin Analogue					Comparator					Comparison Between Groups	Somatostatin Analogue					Comparator					Comparison Between Groups	
	Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		
Halse and Colleagues[36]	13.8 ±5.2 *OGTT 11.2 ± 4.5*	2.9 ± 0.7 *OGTT 2.9 ± 0.9*	-10.9 (-79%) *OGTT -8.3 (-74%)*	<0.01 *OGTT <0.01*	12	18.8 ± 7.5 *OGTT 16.4 ± 8.0*	5.4 ± 1.2 *OGTT 4.4 ± 1.1*	-13.4 (-71%) *OGTT -12 (-73%)*	<0.01 *OGTT <0.01*	11	*Difference in Change:* 2.5* (OGTT 3.7*) *Statistical Comparison:* N/A	3.04 ±0.36	1.43±0.36	- 1.61 (-53%)	<0.01	12	2.93 ±0.4	2.13 ±0.27	-0.80 (-27%)	<0.01	11	*Difference in Change:* 0.81* *Statistical Comparison:* N/A	Health State State: Octreotide sc (GH / IGF-1); Bromocriptine (GH / IGF-1) Normalised GH<2µg/l, IGF-1<1.9U/ml: 4 / 8 / 2 / 4 Improved GH ↓>50% IGF-1 ↓>20%: 6 / 2 / 7 / 3 Unchanged: 2 / 2 / 2 / 4
Ezzat and Colleagues[31,32]	39 ± 11	10 ± 3*	-29 (-74%)	<0.001	52	18.6±4.2*	19.5±2.7*	+0.9 (+5%)	N/S	47	*Difference in Change:*-29.9* *Statistical Comparison:* N/A	5.10 ± 0.40*	2.53 ± 0.40*	- 2.57 (- 50%)	<0.001	52	5.00 ± 0.40*	4.52 ± 0.50*	-0.48 (-10%)	N/S	47	*Difference in Change:* 2.09* *Statistical Comparison:* N/A	N/A
Fredstorp and Colleagues[33-35]	26.9 ±7.7*	9.1 ±3.8*	-17.8 (-66%)	N/A	10	20.3 ±3.9*	19.3 ±4.5*	-1 (-5%)	N/A	10	*Difference in Change:*-16.8* *Statistical Comparison: P*<0.05 for endpoint values	4.26 ± 0.50*	2.59 ± 0.76*	-1.67 (-39%)	N/A	10	4.05 ± 0.33*	3.85 ± 0.39*	-0.2 (-5%)	N/A	10	*Difference in Change:* 1.47* *Statistical Comparison:* N/S for endpoint values	*Health State* 40% in treatment group reached GH<2µg/L and 40% IGF-!<1.9U/ml(M) 2.2(F) U/l, only 2/10 reached these levels for GH and IGF-1. These values for placebo group are unknown. 80% of the treatment group and 0% of the placebo group achieved reductions in GH of >50% 80% in the treatment group and 0% in the placebo group achieved reductions in IGF-1 of >20% 10% of both groups had normal IGF-1 at baseline.

Continued

Study	Secondary Outcomes	Tolerability	Adverse Effects/ Events	Drop Outs	Comments
Halse and Colleagues[36]	*Ring Size:* Small (3%) significant decrease in both groups for both hands. *Symptom Scores:* Significant improvement in both groups (sms201-995 34%, bromocriptine 30%). Headache, depression & vitality more improved with sms201-995. *BP:* significant decrease in systolic and diastolic BP in both groups. *Weight:* Small decrease in both groups only significant in sms201-995 group. *Tumour size:* no evidence of tumour growth/shrinkage in either group except for one bromocriptine patient. *Cholesterol:* significant decrease in sms201-995 group (6.3 to 5.3 mmol/l) no change in other group. *Other:* minor outcomes reported but not reiterated here.	Better in the SMS 201-995 group. P<0.04.	Common in both groups, but limit detail given. bromocriptine group: Constipation common. SMS201-995 treated patients: Diarrhoea: 12/13 (92%), Loose/soft stools/flatulance: Yes but number not stated	SMS 201-995: N=1 Bromocriptine: N=2 At least one drop out from each group could be attributed to treatment	Outcomes quoted here are for last measurement whilst on treatment and not for follow up period post treatment. Where reported by the authors outcome values reverted towards baseline levels during the follow up period in both groups. Patients generally had mild to moderate acromegaly.
Ezzat and Colleagues[31,32]	No significant change in TSH, Total/Free T4, glycosylated haemoglobin levels in either group.	N/A	*Nausea + diarrhoea:* reported but 88% of octreotide group and 33% of placebo group p<0.001.	2 drop outs in each group	Only the first phase of this trial was relevant. Many outcomes not measured/reported for this phase. Variation in IGF-1 levels at baseline between groups – authors state that this is NS.
Fredstorp and Colleagues[33-35]	PRL/TSH/T_3/T_4/blood glucose/urine analysis/white blood cell differential count/routine biochemistry – N/S difference between groups. ECG, BP, body weight and temperature. No major changes observed. Insulin: Octreotide sc: 39.1±5.5 to 23.9±7.1* (N=8) Placebo:39.1±5.5 to 44.9±12.0*(N=10) Oct reotide sc vs Placebo: P<0.05	N/A	Gastrointestinal (diarrhoea, loose/soft stools, abdominal pain/discomfort, pale stools) reported in 70% of octreotide group and 10% of placebo group.	None	Does not measure patient centred outcomes.

*: calculated from authors measurements.

B. Neo-Adjuvant Treatment

Study Characteristics

Study/Reference	Type of Study / Location	Population					Intervention	Comparator	Length of follow up	Major Outcomes	Comments
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments	Other					
Ezzat and Colleagues[37-39]	Randomised parallel multicentre open (single blinded for some outcomes) 17 Centres in Europe, USA & Canada.	Serum GH >2µg/l throughout a 2hr OGTT, pituitary tumour ≥ 10mm dia on MRI or CT	Patients who had undergone pituitary surgery or irradiation, bromocriptine treatment in previous month, known ectopic GHRH hypersecretion	86	N/A		(1) *Drug:* Octreotide acetate *Dose:* 50µg of every 8hr for first week then 100µg every 8hr for remainder of 4 months. *Regime:* Sc injection (2) Surgical resection of tumour *Route:* N/A N=43	Surgical resection of tumour only *Route:* N/A N=43	One month follow up post surgery in both groups	Serum GH Serum IGF-1 Morphology and Histochemistry of excised tumour	Does not report patient centred outcomes. Three publications reporting different outcomes of the same study.
Zgliczynski[40]	Randomised Parallel but assessor blinded for one outcome Location: N/A	Clinical symptoms of acromegaly with pituitary tumour visible on MRI with inablity to reduce serum GH to <2.5µg/l on OGTT and serum IGF-1 > 450µg/l	N/A	50	42 previous untreated 8 unspecified	41 macro-tumours 10-52mm dia. with supra/extrasellar extension	(1) *Drug:* Lanreotide LP *Dose:* 6 x 30mg over 3 months *Regime:* N/A (2) Surgical resection of tumour by *Route:* transphenoidal N=25	Surgical resection of tumour only *Route:* transphenoidal N=25	Follow up unclear in both groups	Serum GH Serum IGF-1 Tumour size, consistency, extension and ease of removal	Does no report patient centred outcomes. Data extracted from a translation of the original French text.

Quality

Study/ Reference	Type of RCT/blinding	No. Patients	Allocation Concealment	Similarity between groups at baseline	Withdrawals stated	ITT	Follow up rates for major outcomes	Jadad Score	Comments
Ezzat and Colleagues[37-39]	Randomised parallel predominantly open but single blinded for morphological outcomes	86	Randomisation, allocation and concealment unclear	Unclear	Unclear	Unclear	Biochemical: Morphology: Unclear – not all tumour samples analysed. Numbers not stated.	2	Numbers of patients do not add up, and it is unclear where the missing patients have gone.
Zgliczynski[40]	Randomised, parallel, predominantly open but assessor blinded for one outcome.	50	Randomisation, allocation and concealment unclear	Unclear however authors state that 'parity' was retained between groups for mean age, gender, duration of acromegaly, plasma GH & IGF-1 and tumour dimension on MRI	Unclear	Yes	100% for GH & IGF-1 in intervention group. Unclear for comparator group.	1	Report lacks detail.

Outcomes

Study	Mean Serum GH + sem (µg/l)											Mean IGF-1 + sem (U/l)											Patient Status
	Somatostatin Analogue + Surgery					Surgery					Comparison Between Groups	Somatostatin Analogue + Surgery					Surgery					Comparison Between Groups	
	Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		
Ezzat and Colleagues[37-39]	49 ± 9	11 ± 6	-38 (-78%)	<0.01	34/43 (79%)	42 ± 14	22 ± 11	-20 (-48%)	<0.017	35/43 (81%)	*Difference in Change:* 18* *Statistical Comparison:* N/A	6894 ± 971	1801 ± 318	-5093 (-74%)	<0.001	34/43 (79%)	8813 ± 1221	5188 ± 1649	-3625 (-41%)	<0.007	35/43 (81%)	*Difference in Change:* 1468* *Statistical Comparison:* N/A	N/A
Zgliczynski[40]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	*Difference in Change:* N/A *Statistical Comparison:* N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	*Difference in Change: N/A Statistical Comparison:* N/A	'Cured' post surgery Lanreotide/Surgery=19/25 (76%) Surgery only=11/25(44%) P<0.05 Definition of 'cured' not given

Continued

Study	Secondary Outcomes	Tolerability	Adverse Effects/ Events	Drop Outs	Comments
Ezzat and Colleagues[37-39]	*Morphology*: No significant difference between groups in tumour profile: No difference in size of cell, cytoplasm, nuclei, nuclei:cytoplasm ration between tumours removed from both groups. No statistical difference between size, nuclei, secretory granules, or lysosomes between groups. N=N/A *Tumour Growth Fraction:* I=0.011 ± 0.004% N=16 C= 0.065 ± 0.016% N=16 P<0.0068. No significant difference between tumour sub-types. *Subgroup Analysis:* DH Tumours: GH reduced to 26 ± 9% of baseline by somatostatin + surgery and to 30 ± 7% by surgery alone. SG Tumours: GH reduced to 24 ± 5% of baseline by somatostatin + surgery and to 37% ± 16 by surgery alone. IGF-1 no difference in extent of reduction of IGF-1 and tumour sub-type in either within and between each treatment arm.	N/A	N/A	None	Biochemical markers: as these outcomes were not measured on all patients the criteria on which patients were selected is unclear. No significant differences between treatment groups with regard to mean age, gender, ethnicity, height, weight and duration of acromegaly. Morphology and histochemistry: Samples showing signs of major membrane damage were excluded from analysis. Numbers of samples excluded are not given. Only densely and sparsely granulated tumours analysed. Bi-hormonal tumours appear not to have been fully analysed. Given selection of samples findings may not be representative.
Zgliczynski[40]	*Tumour Characteristics:* In patients in the intervention group with good response to lanreotide (GH<2.5µg/l on OGTT) tumours were softer, smaller and more favourable to surgery than those in the comparator group. *Subgroup Analysis:* Lanreotide response correlated with those patients who on scinctography had a higher density of somatostatin receptors. Those who did not respond to lanreotide had an absence of receptors.	N/A	N/A	N/A	No patient centred outcomes reported Definition of cured state not given Objective measures of characteristics of extracted tumours do not appear to have been used. Very little information given about outcomes in either group particularly the comparator group.

*: calculated from authors measurements.

C. Primary Treatment

No studies met the inclusion criteria for this section of the review

D. Analogue Comparison

Study Characteristics

Study / Reference	Type of Study / Location	Population					Intervention	Comparator	Length of follow up	Major Outcomes	Comments
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments	Other					
Chanson and Colleagues[42]	Randomised multicentre Open 26 centres in France, Spain, Germany.	N/A	No patient had undergone pituitary irradiation within previous 12 months or pituitary surgery in previous 4 weeks or were receiving dopamine agonist or octreotide sc treatment	125	All patients had been treated with Lanreotide LA 30mg every 10 days (51%) or 14 days (49%) for a mean of 26 months (2-117). 47% had previous pituitary irradiation mean 7 yrs (1-43) prior to study	*Mean age:* 47yrs (18-76) *Sex:* 46%M/54%F *Mean body weight:* 82kg (42-142)	*Drug:* Continue previous lanreotide LA treatment. *Dose:* 30 mg every 10 days or 14 days. *Regime:* im injection N=27	*Drug:* Switch without washout to octreotide LAR. *Dose:* 20 mg monthly *Regime:* im injection N=98	3 months treatment	Serum GH Serum IGF-1 Clinical efficacy Adverse events Tolerability.	2-phase trial. First phase as described and second phase a randomised dose range study of octreotide LAR. As all patients treated with lanreotide LA pre study thus population may be lanreotide/somatostatin analogue sensitive.

Quality

Study/ Reference	Type of RCT/blinding	No. Patients	Allocation Concealment	Similarity between groups at baseline	Withdrawals stated	ITT	Follow up rates for major outcomes	Jadad Score	Comments
Chanson and Colleagues[42]	Randomised multicentre open	125	Concealment unclear	Not matched for number as n=27 in intervention group & n=98 in comparison group. No other information given on characteristics of groups	Yes but cannot be broken down by group due to insufficient information	No	Biochemical efficacy I=78% C=78%, insufficient information given regarding other outcomes	1	Limited information makes it difficult to account for all patients.

Outcomes

Study	Mean Serum GH ± sem (mU/l)											Mean Seum IGF-1 nmol/l											Patient Status / Comments
	Lanreotide LA					Octreotide LAR					Comparison Between Groups	Lanreotide LA					Octreotide LAR					Comparison Between Groups	
	Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		Before	After	Change* (%)	P	N	Before	After	Change* (%)	P	N		
Chanson and Colleagues[42]	9.4 ± 4.4	8.1 ± 3.4	-1.3 (-14%)	<0.801	21/27	9.9 ± 1.3	6.6 ± 0.8	-3.3 (-33%)	N/A	86/98	*Difference in Change:* 2.0* *Statistical Comparison:* N/A	50 ± 5	49 ± 5	-1 (-2%)	<0.187	21/27	59 ± 3	48 ± 3	-11 (-19%)	N/A	86/98	*Difference in Change: 10** *Statistical Comparison: N/A*	*Patient Status - IGF-1 levels normalised:* Lanreotide LA, 11(52%) before and the same after treatment. Octreotide LAR, 42(47%) before and 56(65%) after treatment. *Comment:* Age but not sex taken into account when ascertaining whether patients had normal IGF-1 levels.

Continued

Study	Secondary Outcomes	Tolerability	Adverse Effects/Events	Drop Outs	Comments
Chanson and Colleagues[42]	*Self reported symptoms:* No significant change in either group *Body weight, BP, Pulse:* No significant change in either group	Pain, erythema, swelling at injection site reported by <20% of patients with either analogue and was graded as mild to moderate	*% affected* *Microlithiasis:* Lanreotide LA: before 24%, after 36% Octreotide LAR: before 15%, after 17% *Gallstones*: Lanreotide LA: before 28%, after 14% Octreotide LAR: before 19%, after 21%	*Lanreotide LA:* 1x for tumour resection 1x biliary cholic *Octreotide LAR:* 1 x Death 1x fever on injection 1x depression Other withdrawals unverifiable.	Most of the results of this 2 phase study are reported as the pool of octrotide LAR 20mg/month treatment groups in the first 1 & 2 phase compared with the lanreotide LA group of the 1st phase. This table only contains the results, where they could be isolated, from phase 1. Individual patient data was excluded from the analysis in this trial for a variety of reasons. Many of these reasons were related to incorrect drug administration.

*: calculated from authors measurements

Appendix 10 - Economic Evaluation

Costs

Unit costs for the resources for the various medical adjuvant treatment strategies in acromegaly

Resource	Unit	£	Source
Drug			
Octreotide sc	100µg	5.96	MIMS May 2001
Octreotide LAR*	20mg 30mg	850.00 1062.50	Monthly index of medical specialities[47]
Lanreotide LA*	30mg flat fee: /28days	334.25 668.50	Monthly index of medical specialities[47] Ipsen Ltd (Desson A, Ipsen Ltd, Maidenhead, UK: personal communication, 2001)
Bromocriptine	2.5mg x 30 / 2.5mg	5.28 0.176	Monthly index of medical specialities[47]
Cabergoline	500µg x 8	30.04 (3.76 / 500µg)	Monthly index of medical specialities[47]
Disposables			
Sc injection kit	Syringe, Needle, Swab, use of sharps bin	0.10	Huntleigh Direct[59]
Monitoring			
IGF-1 Test	blood extraction x 1 laboratory test x 1	0.80 29.10	(Lewis P & Roper J, Birmingham University Hospital NHS Trust, UK: personal communications, 2001)
GH Oral Glucose Tolerance Test	blood extraction x 1 laboratory test x 1	0.80 7.70	(Lewis P & Roper J, Birmingham University Hospital NHS Trust, UK: personal communications, 2001)[47]
Out Patient Ultrasound Scan of Gall Bladder	1	38.00	(Office of the Superintendent of Radiology, Birmingham University Hospital NHS Trust, UK: personal communication, 2001)
Appointments			
Out Patient Appointment	1	74.00 (56-84)	National Schedule of Reference Costs 2000[48]
Staff			
Staff Nurse	/hour /5 minutes	31.00 2.58	Unit Costs of Health and Social Care 2000[60]
Nurse Advisor	/ im injection	0	Ipsen Ltd(Desson A, Ipsen Ltd, Maidenhead, UK: personal communication, 2001)

* Supplied with diluent, syringe and needles.

Assumptions

A number of assumptions were made with regard to apportioning resources and their subsequent costs. These are detailed below:

- Staff costs include components to reflect investment in pre and post registration education, overheads (including capital overheads) and ongoing training, and were derived from the costs for patient related activities/contact.
- Staff nurse resources were costed at day ward rates.
- Training patients to self inject with octreotide sc was valued as 30 minutes hour of staff nurse time plus two syringe/needle/swab kits.
- The cost of equipment for self injection was estimated as a combination of one needle, one syringe,one swab per injection and one sharps bin per patient.
- The dose of octreotide sc is 100-200µg three time per day. 150µg was taken as the mean with 100-200µg as the range.[22] The initial dose of octreotide LAR is 20mg/28days for 3 months then adjusted to 10-30mg/28 days depending on patient response and side effects. 20mg was taken as the mean dose and 10-30 as the range.[22] The initial dose of lanreotide LA is 30mg/14 days and adjusted after three months to 30mg every 7 to 14 days depending on patient response and side effects. The ten day interval was taken as the mean interval with 7 and 14 days as the range.[22] The dose of bromocriptine is 10-30mg daily with 20mg taken as the mean.[22] The dose of cabergoline is 1-4.5mg weekly with 1.75 mg taken as the mean.[22,58]
- Administration of depot somatostatin analogues was estimated to require 5 minutes of staff nurse time.
- Patients treated with somatostatin analogues have an ultra-sound examination of the gall bladder before initiation of treatment and at 6 monthly intervals thereafter.
- The frequency of monitoring and biochemical marker used for monitoring appears to vary between centres. Therefore three outpatient consultant appointments and IGF-1 tests per year were assumed, plus an additional consultant appointment and IGF-1 test at the end of the two week assessment of responsiveness to octreotide sc for patients treated with somatostatin analogues.
- An IGF-1 test was on a single blood sample. The cost of the alternative, an oral glucose tolerance test for GH, assuming the taking and testing of 5 blood samples, would be about 70% more expensive than an IGF-1 test.
- The taking of a blood sample comprises 1/12 the hourly rate for a phlebotomist plus materials (Roper J, Birmingham University Hospital NHS Trust, UK: personal communications, 2001).
- Octreotide LAR and lanreotide LA injections can be administered at a number of geographical locations (outpatient clinic, GP practice or patients convenient location) and by different health care staff, depending on which analogue is being given and whether it is administered as part of a shared care protocol or a pharmaceutical company scheme. For the purpose of this analysis the outpatient clinic was assumed to be the venue with administration taking a staff nurse 5 minutes. Ipsen Ltd the suppliers of Lanreotide LA operate a Nurse Adviser Service, which includes availability of nurse advisors to give the im injections at a time and place convenient for the patient or training for practice staff in the delivery of these injections. The use of this free scheme has been built into the sensitivity analysis. No such schemes exists for octreotide sc or LAR
- Lanreotide LA can be supplied by Ipsen Ltd at a flat monthly fee irrespective of dose. The fee is equivalent to 30mg every 14 days for 28 days and represents a saving for patients on more frequent dosing regimes. This pricing structure has been incorporated in to the analysis.
- Costs were not adjusted to allow for any brief period of dose escalation on initiation of treatment with either octreotide sc or the dopamine agonists, as the variation in cost would be small compared to the annual costs.
- The cost of the outpatient appointment at which a decision on which strategy to follow was made is not included as this would be the same for all strategies and occur prior to initiation of treatment. Any monitoring or procedures at this stage were considered as routine for acromegaly patients having undergone pituitary surgery or radiotherapy and not specific to subsequent medical treatment. Therefore these are excluded from the analysis.
- Summary costs have been rounded to the nearest £.

Summary cost for treatment strategies

Time	Type of Resource	Treatment			
		Somatostatin Analogues		Dopamine Agonist	
		Octreotide	Lanreotide	Bromocriptine	Cabergoline
0-2weeks	Drug	Octreotide sc 100-200µg £375(250-501)	Octreotide sc 100-200µg £375(250-501)	Bromocriptine 10-30mg/day £20 (10-30)	Cabergoline 1-4.5mg/week £26 (15-68)
	Administration	Injection Kits £4	Injection Kits £4	£0	£0
		Training of patient in self administration of sc injection £16	Training of patient in self administration of sc injection £16	£0	£0
	Appointments	£74 (56-84)	£74 (56-84)	£0	£0
	Monitoring	£68	£68	£0	£0
	Subtotal	**£537 (394-672)**	**£537 (394-672)**	**£20 (10-30)**	**£26 (15-68)**
Weeks 3-14	Drug	Octreotide LAR 20mg £2550	Lanreotide LA 30mg/14days £2006 (CA £2006)	Bromocriptine 10-30mg/day £118 (59-177)	Cabergoline1-4.5mg/week £158 (90-406)
	Administration	Staff Nurse £8	Staff Nurse £16 (NAv £0)	£0	£0
	Appointments	£74 (56-84)	£74 (56-84)	£74 (56-84)	£74 (56-84)
	Monitoring	£30	£30	£30	£30
	Subtotal	**£2662 (2644-2672)**	**£2125 (2107-2135) CA 2125 (2107-2135) CA+NAv £2109 (2091-2119)**	**£222 (145-291)**	**£262 (176-520)**
Weeks 15-52	Drug	Octreotide LAR 10-30mg £8075 (6056-10094)	Lanreotide LA 30mg/7-14 days £8891 (6351-12702) (CA £ 6351)	Bromocriptine 10-30mg/day £375 (187-562)	Cabergoline1-4.5mg/week £500 (286-1286)
	Administration	Staff Nurse £25	Staff Nurse £69 (49-99) (NAv Service £0)	0	0
	Appointments	£148 (112-168)	£148 (112-168)	£148 (112-168)	£148 (112-168)
	Monitoring	£98	£98	£60	£60
	Subtotal	**£8346 (6291-10384)**	**£9206 (6610-13066) CA £6666 (6610-6715) CA+ NAv 6597(6561-6617)**	**£582 (359-790)**	**£708 (458-1514)**
Year 1	**Total**	**11545 (9329-13728)**	**11868 (9111-15874) CA 9328 (9111-9523) CA+Nav 9243 (9046-9408)**	**824 (514-1110)**	**996 (649-2101)**

CA: using flat monthly fee for purchase of lanreotide LA irrespective of dose;
NAv: using free Nurse Advisory Service to give intramuscular injections of Lanreotide LA.

Modelling

Due to the lack of relevant randomised trials, the modelling of the incremental costs per life year saved and the incremental costs per QALY utilised studies identified from various parts of this review and these were predominantly cohort studies. The findings of these with regard to the frequency of GH level at last follow up in each study for each intervention are listed in the table below within the GH range specified in the study.

Mean frequency (range) of GH level at last follow up* by category reported

Drug	Summary Mean Frequency (± range) in each GH category expressed as % of study population. (n= number of studies contributing data)									
	<2µg/l	<2.5µg/l	<5µg/l	2-5µg/l	2.5-10µg/l	>2µg/l	>2.5µg/l	>5µg/l	5-10µg/l	>10µg/l
Octreotide	30 (22-38) n=2[50,51]	67 (67-67) n=1[52]	53 (45-61) n=2[51,53]	23 (23-23) n=1[51]	31 (31-31) n=1[52]	70 (62-78) n=2[50,51]	33 (33-33) n=1[52]	47 (39-55) n=2[51,53]	29 (29-29) n=1[53]	14.5 (3-26) n=2[52,53]
Lanreotide		40 (34-46) n=3[54-56]			53 (53-53) n=1[56]		60 (54-66) n=3[54-56]			13 (13-13) n=1[56]
Cabergoline	37 (28-46) n=2[57,58]		64 (56-73) n=2[57,58]	27 (27-28) n=2[57,58]				36 (27-44) n=2[57,58]		
Bromocriptine			20 (20-20) n=1[21]					80 (80-80) n=1[21]	31 (31-31) n=1[21]	49 (49-49) n=1[21]
No Treatment*	0 (0-0) n=4[52,56-58]	0 (0-0) n=4[51,52,56,57]	17 (3-44) n=5[51,52,56-58]	17 (3-44) n=5[51,52,56-58]	41 (17-61) n=4[51,52,56,57]	100 (100-100) n=4[52,56-58,58]	100 (100-100) n=4[51,52,56,57]	83 (57-97) n=5[51,52,56-58]	27 (14-41) n=5[51,52,56-58]	56 (40-83) n=5[51,52,56-58]

*Values for the no treatment group were derived from the baseline values reported in the studies. It should be noted that a large proportion of patients in these studies had been on medical treatment prior to baseline measurement. Although some studies utilised a wash out period before baseline measurement the data could over estimate the efficacy of no treatment.

The table above highlights the large number of categories of final GH level that the studies report. The model was based on the GH categories <2.5µg/l, 2-5-10µg/l and >10µg/l as a GH level <2.5µg/l is considered to be a normal level and data for mortality for these categories was available.

It was decided that data for octreotide sc, octreotide LAR and lanreotide LA would be combined to give values for the somatostatin analogue class. This was deemed acceptable due to the perceived similar efficacy of these drugs. Data for bromocriptine and cabergoline were not combined to form dopamine agonist class, as their efficacy is not perceived to be similar.

Given the range of categories of final GH level reported in the cohort studies and the absence of data for some categories, where necessary the available data was fitted to the categories chosen for the model (eg information from both the <2µg/l & <2.5µg/l categories were used to populate the <2.5µg/l category in the model).

The point estimates and ranges for the populations in each GH category utilised in the model are given in the table below. Given that a GH level of <2.5µg/l is accepted as being normal the estimated uncertainty for the effectiveness data were driven by the range of frequency values in the cohort studies for the GH level <2.5µg/l category (e.g. range for octreotide/lanreotide combined =22-67). As the sum of the percentage frequencies across categories for each treatment must equal 100, the range for the other two categories (2.5-10 & >10µg/l) was calculated proportionally using the point estimates for the same categories (e.g. for octreotide/lanreotide combined 22-52 (2.5-10µg/l) and 11-26 (>10µg/l), so that the most beneficial assessment of the intervention across all three categories was 67(2.5µg/l) + 22 (2.5-10µg/l) + 11 (>10µg/l) and the least beneficial was 22 + 52 + 26 respectively).

Frequency point estimate and range for population in each GH category for use in sensitivity analysis

Drug	Frequency (± range) in each GH category expressed as % of study population for point estimate and sensitivity analysis		
	<2.5µg/l	**2.5-10µg/l**	**>10µg/l**
Octreotide (sc & LAR) & Lanreotide LA Combined	40 **(22-67)** *(22-67)*	40 **(22-52)** *(31-53)*	20 **(11-26)** *(3-26)*
Cabergoline	35 **(28-46)** *(28-46)*	35 **(29-39)** *(27-72)*	30 **(25-33)** *(0-36)*
Bromocriptine	10 **(0-20)** *(0-20)*	40 **(36-44)** *(20-80)*	50 **(44-56)** *(30-80)*
No Treatment	0 **(0-0)** *(0-0)*	40 **(20-60)** *(17-61)*	60 **(40-80)** *(40-83)*

Figures in *italics* represent the frequency ranges assumed from the raw data presented in the table at the top of this page as opposed to the ranged in **bold** which were used in the model and which have been fitted to ensure that the population across outcome categories for each treatment equals 100%.

Treatment costs and uncertainty around them were as per the second year of treatment reported in the current systematic review except for the cost of no treatment, which was taken to be zero. We assumed that any other interventions given would be identical in all respects for all four groups and therefore need not be considered. Although we acknowledge that this may not be the case where additional, treatment or care may be required to alleviate symptoms of acromegaly in the case of no treatment or to deal with adverse effects of active drugs. The second year costs for octreotide and lanreotide were averaged to give the costs for the somatostatin analogue group. For the uncertainty around the costs for this group, the maximum and minimum possible costs were used rather than the range for an individual preparation.

Quality of life data had to be assumed given the limited empirical data available. Uncertainty around the point estimates was also assumed and the estimates are outlined in the table below.

Assumed Quality of Life for each GH category

GH Category	Quality of Life	Range
Population	1.00	
<2.5µg/l	0.95	0.85-1.00
2.5-10µg/l	0.80	0.70-0.95
>10µg/l	0.70	0.50-0.80

Population mortality data was estimated according to the 1991-95, male and female 40-45 category[49] at 1.67/1000. Standard mortality ratios for the different GH categories were taken from Orme *et al* (1998)[14] and were GH<2.5µg/l: 1.1, 2-5-10µg/l: 1.41 and >10µg/l: 2.12
Mortality for each category was calculated as the population mortality multiplied by the standard mortality ratio for that category.

Deaths for each treatment were calculated as the sum of the mortality rate for each outcome category multiplied by the proportion of patients in that category.

Incremental lives saved were calculated by subtracting the deaths in the treatment group from the chosen reference value.

Incremental costs per life year saved were calculated by dividing the cost for the treatment by the incremental lives saved.

QALYs for each treatment were calculated as the sum of the product of the proportion of survivors in each category and by the QALY for that category. Where the proportion of survivors was calculated as proportion in the category multiplied by 1 minus the mortality for that category.

Incremental QALYs were calculated by subtracting the QALYs in the treatment group from the chosen reference value.

Incremental costs per QALY were calculated by dividing the cost for the treatment by the incremental QALYs.

Sensitivity Analysis

In the incremental cost utility calculations, there is great uncertainty in the effectiveness estimates, the quality of life assumed and the costs. The likely range of these uncertainties is given in the tables above.

All these uncertainties were incorporated into a sensitivity analysis to give a range of incremental cost per life year saved and cost per QALY values. The analysis combined the uncertainties to give the most optimistic and most pessimistic estimates for these outcomes. For example, for the most pessimistic scenario, the lowest estimates of effectiveness were combined with the highest estimate of costs. For the most optimistic scenario, the highest estimates of effectiveness were combined with the lowest estimate of costs.

The table below outlines the findings of the modelling and the associated sensitivity analysis.

Data Utilised and Results of Modelling Incremental Costs per Life Year Saved and Costs per QALY Saved

	Mortality	Index QALY	Somatostatin Analogue	Cabergoline	Bromocriptine	No treatment
Population	0.00167	1.00	**Frequency of GH level after treatment**			
<2.5 µg/l	0.00184	0.95 (0.85-1.00)	0.4 (0.22-0.67)	0.35 (0.28-0.46)	0.1 (0.0-0.20)	0.0 (0.0-0.0)
2.5-9.9µg/l	0.00235	0.80 (0.70-0.95)	0.4 (0.22-0.52)	0.35 (0.29-0.39)	0.4 (0.36-0.44)	0.4 (0.20-0.60)
>=10.0 µg/l	0.00354	0.70 (0.50-0.80)	0.2 (0.11-0.26)	0.30 (0.25-0.33)	0.5 (0.44-0.56)	0.6 (0.40-0.80)
Cost/year			10,322 (8,655-17,934)	996 (649-2,101)	824 (514-1,110)	0 (0-0)
Deaths			0.002384 (0.0025472-0.002139)	0.0025285 (0.0026-0.002413)	0.002894 (0.003016-0.002772)	0.003064 (0.003302-0.002826)
Lifes saved						
Incremental			0.00068 (0.0007548-0.000687)	0.0005355 (0.000702-0.000413)	0.00017 (0.000286-5.44E-05)	Reference
Incremental			0.00051 (0.0004692-0.000632)	0.0003655 (0.000417-0.000359)	Reference	
Incremental			0.0001445 (5.27E-05 - 0.000274)	Reference		
Costs/LYsaved						
Incremental			15,179,412 (12,601,922-23,759,936)	1,859,944 (1,571,048-2,992,451)	4,847,059 (9,448,529-3,886,555)	Reference
Incremental			18,623,529 (12,873,182-35,856,777)	470,588 (376,359-2,379,352)	Reference	
Incremental			64539792 (29,251,005-300,436,433)	Reference		
QALYs			0.83805 (0.96496-0.67934)	0.82049 (0.93330-0.67434)	0.76283 (0.89158-0.58629)	0.73776 (0.53826-0.88753)
QALY saved						
Incremental			0.10029 (0.07744-0.14109)	0.08273 (0.04577-0.13608)	0.02507 (0.00405-0.04803)	Reference
Incremental			0.07522 (0.07338-0.09306)	0.05765 (0.04172-0.08805)	Reference	
Incremental			0.01757 (0.03167-0.00500)	Reference		
Cost/QALY						
Incremental			102,919 (111,769-127,115)	12,040 (14,179-15,439)	32,864 (23,111-126,772)	Reference
Incremental			126,271 (110,940-180,796)	2,983 (3,236-11,255)	Reference	
Incremental			530,900 (252,824-3,164,138)	Reference		