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Pituitary Disorders
Drug Treatment Options

John J. Orrego and *Ariel L. Barkan*

Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan, USA

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Abstract

Pituitary diseases are relatively common entities in the general population. They include pituitary adenomas and hypopituitarism. Pituitary tumours can cause symptoms of mass effect and hormonal hypersecretion that can be reversed with surgical resection or debulking of the adenoma, radiotherapy, or medical treatment. Transsphenoidal adenomectomy is the treatment of choice for acromegaly, Cushing's disease, gonadotropin-secreting tumours; and thyrotropin (TSH)-secreting

adenomas. Pituitary irradiation and medical therapy are secondary options. Conversely, medical treatment is the primary choice for prolactinomas. Dopamine agonists are very effective in the treatment of prolactin (PRL)-secreting tumours, with rates of control as high as 80 to 90% for microprolactinomas (<10mm) and 60 to 75% for macroprolactinomas (≥10mm). Somatostatin analogues have also shown efficacy in patients with acromegaly who have not responded to surgery or in patients with TSH-secreting adenomas who have not improved with surgery and radiotherapy. In patients with Cushing's disease, who are not cured surgically or who relapse after pituitary adenomectomy and irradiation, steroidogenic inhibitors can be an efficient method of controlling the hypercortisolism.

Pituitary insufficiency is the partial or complete loss of the anterior hypophyseal function, which is due to hypothalamic or pituitary disease. Although the classic sequence of loss of pituitary secretion is growth hormone (GH), gonadotropins, TSH, and corticotropin (ACTH), the order to begin the replacement therapy of the deficient hormone(s) is cortisol, thyroxine, androgens/estrogens and, if necessary, GH. There are multiple preparations that can be used to achieve clinical and biochemical improvement. In general, the hormone replacement therapy is lifelong.

1. Pituitary Adenomas

1.1 Prolactin-Secreting Adenomas

60% of all functioning pituitary tumours are prolactinomas. 90% of patients with microprolactinomas (10mm) are women and 60% with macroprolactinomas (10mm) are men. Women of reproductive age frequently come to medical attention because of oligo/amenorrhoea, infertility and galactorrhoea. Men and postmenopausal women usually present with symptoms of a pituitary mass (headache and visual abnormalities).[1] Serum prolactin (PRL) levels are always above 200 μg/L in patients with macroadenomas, but may be only moderately increased in patients with microadenomas.

Observation may be justified in women with microadenomas who do not desire pregnancy or do not have significant galactorrhoea; or in men with microprolactinomas who do not have clinical or biochemical hypogonadism. To avoid osteoporosis in women with oligo/amenorrhoea, oral contraceptives can be prescribed without risk of increasing tumour size.[2] Patients with macroprolactinomas always require therapy to prevent or reverse tumour mass effect.

The objectives of therapy for prolactinomas are normalisation of PRL levels, reduction in adenoma size, restoration of pituitary function and prevention of recurrence. Medical therapy is the treatment of choice for micro or macroprolactinomas.[3]

Transsphenoidal surgery may be indicated in patients with prolactinomas who do not respond to or tolerate drug treatment, and in patients with psychiatric illness who need neuroleptic agents (concomitant dopamine agonists may precipitate psychotic episodes). Radiation therapy plays a limited role in the treatment of prolactinomas, and may be used when medical treatment and pituitary surgery have been ineffective in stopping the tumour growth. Figure 1 outlines a proposed treatment strategy for prolactinomas.

1.1.1 Dopamine Agonists

Dopamine is the predominant physiological PRL inhibitory factor. Thus, dopamine agonists are utilised to treat hyperprolactinaemia. Bromocriptine is a semisynthetic ergot alkaloid with D_1 and D_2 receptor agonist properties. The suppression of PRL secretion depends on the number and affinity of tumour dopamine receptors. Bromocriptine should be started at a low dosage (0.625 to 1.25mg taken orally with a snack at bedtime) to minimise its adverse effects (nausea, vomiting and postural hypotension). This dosage should be increased by 0.625 to 1.25mg every 3 days, to reach 2.5mg twice daily, and further as needed to normalise PRL levels.

Bromocriptine normalises PRL levels in 80 to 90% of patients. Furthermore, the drug decreases macroadenoma size substantially in 60 to 75% of patients, and restores gonadal function in 80 to 90% of microprolactinoma patients and 60 to 75% of macroadenoma patients.[4,5] Once the pathology is under control, the dosage of bromocriptine can be reduced to the lowest effective dosage for lifelong maintenance. If adverse gastrointestinal (GI) effects are unacceptable, bromocriptine can be given intravaginally to avoid first liver passage. In this case, the dosage may be reduced (2.5 mg/day).[6] A long-acting release bromocriptine preparation (Parlodel LAR®: 50 to 75mg intramuscular injection every 4 to 8 weeks) is also available in some countries. This formulation causes the same adverse effects as the oral formulation, but only for the first few days after administration.[7] Resistance to bromocriptine is observed in 5 to 18% of patients with prolactinomas, which may be explained by a decrease in D_2 receptors or a postreceptor defect.[8]

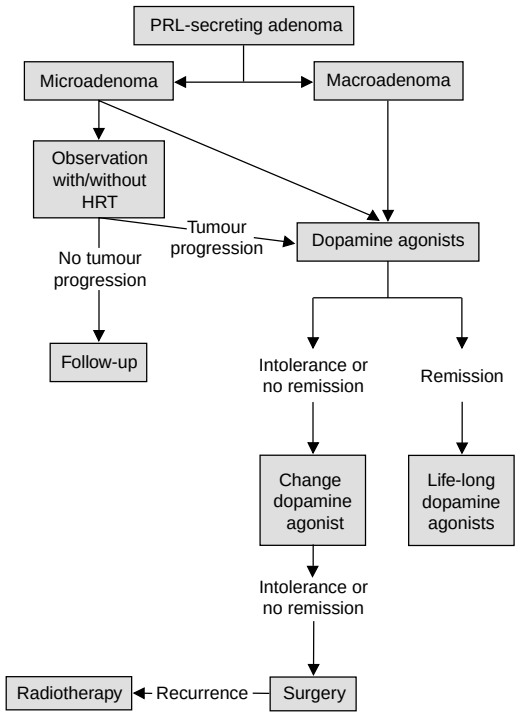

Fig. 1. Proposed treatment strategy for prolactinomas. Remission: PRL <20 μg/L. **HRT** = hormone replacement therapy; **PRL** = prolactin.

Cabergoline, an ergoline derivative, has higher affinity for the D_2 receptor than bromocriptine and a prolonged duration of action. In a double-blind study in 459 women with hyperprolactinaemic amenorrhoea (279 of whom had a microprolactinoma), normoprolactinaemia was achieved in 83% of women treated with cabergoline and 59% of those treated with bromocriptine. Three and 12% of patients withdrew from the respective groups because of drug intolerance.[9] In several series that included 130 prolactinoma patients, 25% of cabergoline recipients had a greater than 50% reduction in tumour size, and 47% experienced a 25 to 50% tumour shrinkage.[10] Usual oral cabergoline dosages are 0.5 to 1.0mg once or twice a week. In addition, cabergoline may be useful in patients with prolactinomas resistant to bromocriptine or quinagolide.[11]

Pergolide is an ergot derivative with a duration of action greater than 24 hours. The usual starting oral dosage is 0.05 mg/day which can be increased to 0.3mg once a day. Pergolide normalises hyperprolactinaemia and shrinks most prolactinomas. Its adverse effects are similar to those of bromocriptine. The drug may be also useful in patients with prolactinomas resistant to bromocriptine.[12]

Lisuride is an ergot derivative which has been effective in reducing the size of macroprolactinomas when administered at an oral dosage of 0.4 to 2.0 mg/day (given 3 or 4 times per day). Adverse reactions are similar to those of other dopamine agonists.[5,13]

Quinagolide (CV 205 502) is a long-acting non-ergot octahydrobenzyl(g)-quinoline with specific D_2 receptor activity. It reverses hyperprolactinaemia and reduces tumour size in patients with macroprolactinomas when used orally at a dosage of 0.1 to 0.4mg once daily. These effects are associated with improvement of visual abnormalities and restoration of gonadal function.[14]

Other dopamine agonists tested for the treatment of prolactinomas include terguride (a lisuride derivative), metergoline (an antiserotoninergic agent), mesulergine, lergotrile, dihydroergocryptine and hy-

dergine.[15] However, these do not offer any advantages over bromocriptine and are not used clinically.

As mandated by the manufacturer, dopamine agonists should be stopped once pregnancy is confirmed. However, bromocriptine and cabergoline have not been found to cause any increase in spontaneous abortions, congenital malformations, ectopic pregnancies or multiple births. Discontinuation of bromocriptine should be followed symptomatically in pregnant women because it is possible that adenoma size may increase (in 2 to 6% of patients with microprolactinomas and 15 to 35% of patients with macroprolactinomas).[10]

1.1.2 Somatostatin Analogues

Prolactinomas contain several subtypes of somatostatin (sst) receptors subtypes – sst_1, sst_2, sst_3, sst_5. Octreotide and lanreotide bind efficiently to sst_2 and with lower affinity to sst_5. They do not alter *in vivo* PRL levels. The receptor sst_5 appears to regulate PRL secretion from prolactinoma cells. Thus, somatostatin analogues (BIM-23052 and BIM-23268) with improved selective binding affinity for these receptor subtypes, may prove to be effective in the treatment of PRL-secreting adenomas.[16]

1.2 Growth Hormone (GH)-Secreting Adenomas

Growth hormone (GH)-secreting adenomas (75% of which are macroadenomas) account for 20% of functional pituitary tumours and their manifestations are either acromegaly or gigantism. Acromegaly has an annual incidence of at least 3 to 4 cases per million and a prevalence of 40 to 90 cases per million. It is a cosmetically disfiguring disease characterised by bony and soft tissue overgrowth, which results in increased hand, foot, and hat size, macroglossia, prognathism, frontal bossing, and coarsening of facial features. Hypertension, diabetes mellitus, sleep apnoea and cardiomyopathy are also more prevalent in patients with acromegaly than in the general population. People with acromegaly have mortality rates that are 2 to 3 times higher than in the general population.[17]

Figure 2 shows a proposed strategy for the treatment of GH-secreting adenoma. The primary goals of treatment are to reduce GH levels below 1 μg/L during a 2-hour oral glucose tolerance test (OGTT) and normalise insulin-like growth factor (IGF)-1 levels (age and gender matched), stabilise or reduce tumour size, and maintain or recover pituitary function. Transsphenoidal resection of the adenoma is the treatment of choice. When it is performed by a skilled neurosurgeon, 50% of patients with macroadenomas and 80% of those with microadenomas will achieve GH levels below 5 μg/L.[17]

External radiotherapy prevents tumour regrowth and slowly (over 5 to 15 years) reduces plasma GH levels, often to the 2 to 5 μg/L range. It is relatively ineffective in normalising plasma IGF-I levels.[18] Radiosurgery (γ-knife) may reduce plasma GH levels more rapidly, but it is still uncertain whether radiosurgery is more effective than external radiotherapy in normalising plasma IGF-I levels.

1.2.1 Somatostatin Analogues

Octreotide is a long-acting synthetic somatostatin analogue that has 10 times higher affinity for sst_2 than for ssT_5. It is also 40 times more potent than somatostatin in suppressing GH secretion. Octreotide suppresses GH levels to <2 μg/L in 40% of patients and normalises IGF-I levels in 60%, and therefore improves many manifestations of acromegaly. The drug has a modest effect on tumour shrinkage; 10% of patients do not respond.

Short term adverse effects include diarrhoea, fat malabsorption, nausea and flatulence. After several months of therapy, 25% of patients will develop asymptomatic gallbladder stones.

Octreotide 100 to 500μg is usually administered subcutaneously 3 times daily depending on the individual response of each patient.[19-21] A continuous subcutaneous pump infusion (up to 600 μg/day)[22] or long-acting octreotide (Sandostatin LAR Depot®; 20 to 40mg intramuscular injection every 4 to 6 weeks)[23,24] have been shown to be effective and well tolerated treatments for acromegaly.

Slow release lanreotide reaches peak plasma concentrations 2 hours after intramuscular injection of a 30mg dose, with gradual reduction over the next 48 hours. Subsequently, drug concentrations increase again and progressively decrease until day 10 to 14 after the injection. Thus, this formulation is administered every 1 to 2 weeks and its efficacy

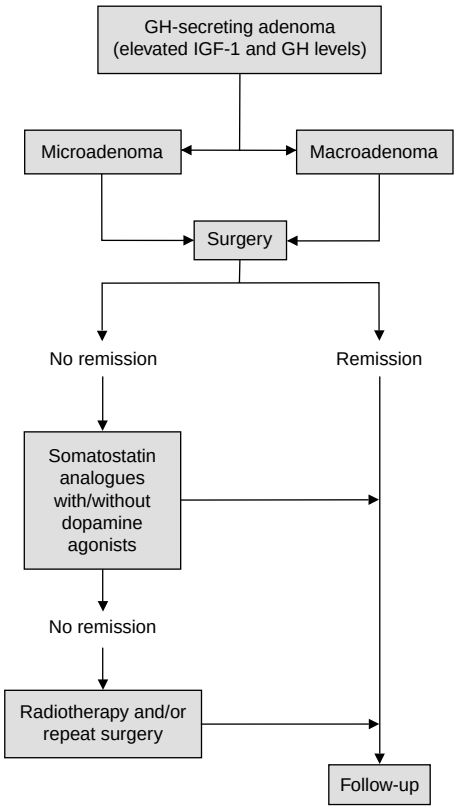

Fig. 2. Proposed treatment strategy for acromegaly. Remission: GH levels <1 μg/L during a 2-hour OGTT and normal IGF-I levels (age and gender matched). **GH** = growth hormone; **IGF-I** = insulin-like growth factor-I; **OGTT** = oral glucose tolerance test.

and tolerability profiles are similar to those of octreotide.[25]

Novel sst_2- and sst_5-selective analogues, with improved receptor affinity, could be a better option for the treatment of acromegaly in the near future.[16]

1.2.2 Dopamine Agonists

Bromocriptine binds to pituitary D_2 receptors and suppresses GH secretion in some patients with acromegaly. Oral administration and low costs are 2 main advantages of dopamine agonists. Unfortunately, bromocriptine 7.5 to 80 mg/day (3 or 4 times daily) only suppresses plasma GH levels below 5 μg/L in 20% of patients and normalises IGF-I levels in 10%. In addition, the majority of somatotroph adenomas will not shrink during therapy and adverse effects are common because larger dosages are used.[26]

Cabergoline 1.0 to 2.0 mg/week may be effective in acromegaly, especially if the pituitary adenoma cosecretes GH and PRL.[27] But in general it is not more effective than bromocriptine for the treatment of this entity.[28]

Quinagolide 0.3 to 0.6 mg/day has been shown to normalise circulating GH and IGF-I levels in some patients with acromegaly, although the rate of adenoma shrinkage has been poor.[28]

1.2.3 Combined Regimens

The combination of somatostatin analogues with dopamine agonists (e.g. octreotide with bromocriptine or quinagolide) has been shown to be equally or more effective in patients with acromegaly than either drug alone.[29,30] This regimen may be useful after surgery and/or radiation therapy in patients with active acromegaly who have had only partial improvement with one of the medications.

1.2.4 GH Antagonists

Human GH (hGH) analogues contain changes in the third α-helix (which forms binding site 2 in hGH) and act as GH antagonists by decreasing the dimerisation of the GH receptor.[31] Pegvrisomant (B2036-PEG) is a pegylated hGH analogue which has improved binding to site 1 and a single amino acid mutation in the binding site 2. This drug was used in 46 patients with acromegaly in a multicentre research study, and appeared to be a well tolerated and potentially useful therapy with a subcutaneous route of administration.[32] Longer studies are necessary to demonstrate its efficacy.

1.2.5 GH-Releasing Hormone Antagonists

(N-Ac-Tyr^1,D-Arg^2)GHRH(1-29)NH_2 (GHRH-Ant) is an analogue of growth hormone-releasing hormone (GHRH) that functions as a competitive antagonist at the level of the GHRH receptor. Intravenous GHRH-Ant suppressed integrated total and pulsatile GH secretion in healthy young men,[33] and briefly lowered elevated GH levels in a patient with acromegaly resulting from ectopic GHRH secretion.[34] The role of this experimental medication in the treatment of acromegaly is still unknown.

1.3 Corticotropin-Secreting Adenomas

Cushing's disease, the excessive secretion of corticotropin (ACTH) by a pituitary corticotroph tumour, is responsible for two-thirds of all cases of Cushing's syndrome. 15% of all functional pituitary tumours are ACTH-secreting adenomas (90% of which are microadenomas). Women are more frequently affected than men (3 to 8 : 1). Cushing's syndrome is characterised by centripetal obesity, moon facies, easy bruisability, proximal myopathy, osteoporosis, psychiatric disturbances, and glucose intolerance. Multiple tests in a logical sequence are necessary to determine the cause of the hypercortisolism.[35]

The treatment of choice for Cushing's disease is selective transsphenoidal adenomectomy after accurate preoperative localisation of the tumour. It has a cure rate of 80 to 90% for microadenomas and 50% for macroadenomas. If a tumour is not visible, either a total hypophysectomy or a hemihypophysectomy is usually performed. Patients who are not cured by surgery or who relapse can receive external pituitary irradiation and/or medical therapy (fig. 3). Complete remission during a median follow-up of 42 months was achieved in 83% of patients who received external pituitary irradiation after persistent or recurrent Cushing's disease, following a transsphenoidal surgery.[36] Medical therapy includes steroidogenic inhibitors, neuromodulators of ACTH release, and glucocorticoid receptor-blocking agents.[37]

In the past, the treatment of choice for Cushing's disease was bilateral adrenalectomy. However, it caused a growth of the residual pituitary tumour with high plasma ACTH levels and hyperpigmentation (Nelson's syndrome) in 10 to 30% of patients. Surgery and/or pituitary irradiation are the treatments of choice, although some patients do not respond to these approaches.

1.3.1 Steroidogenic Inhibitors

Ketoconazole, an antifungal agent, normalised urinary free cortisol (UFC) or urinary 17-hydroxycorticosteroids in 81% of patients with Cushing's disease when administered orally at a dosage of 300 to 400mg twice daily for 0.5 to 8 months. Adverse reactions included elevated transaminases, gynecomastia, GI disturbances, oedema, and skin rash.[37]

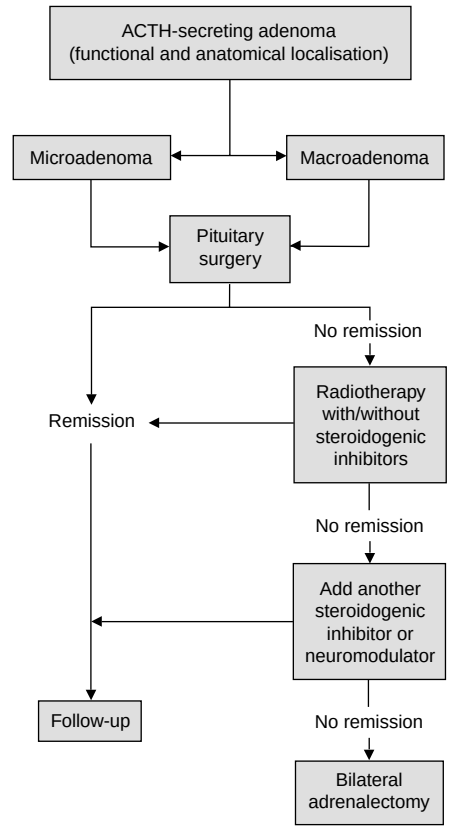

Fig. 3. Proposed treatment strategy for Cushing's disease. Remission: UFC levels <90 μg/24h and morning cortisol levels <5 mg/L after overnight dexamethasone 1mg. **ACTH** = corticotropin; **UFC** = urinary free cortisol.

In a recent paper from Italy, ketoconazole improved UFC levels in 85% of patients with Cushing's disease, including normalisation of UFC levels in 43% of them.[38] Currently, ketoconazole is the preferred pharmacological modality in patients with Cushing's syndrome.

Mitotane (o,p'-DDD) inhibits cortisol hypersecretion by destroying adrenocortical cells and inhibiting 11β-hydroxylase and cholesterol side-chain cleavage enzymes. In a study of nonsurgical therapy, oral mitotane 8 to 12 g/day achieved remission in 82% of patients with Cushing's disease after 8 months of therapy, and in 100% of patients who also received cobalt pituitary irradiation. Overall,

Cushing's disease was controlled in two thirds of patients with or without pituitary irradiation, and adrenalectomy was avoided. Adverse effects included GI distress, gynecomastia, abnormal liver function tests, hyperlipidaemia, and hypoaldosteronism.[39]

Etomidate, an anaesthetic drug, is a substituted imidazole derivative which inhibits the adrenal enzymes 11β-hydroxylase and desmolase. A 0.1 mg/kg/h intravenous infusion of etomidate rapidly reduced hypercortisolaemia in patients with Cushing's disease without significant adverse effects.[40] This drug is therefore an attractive choice to rapidly correct severe hypercortisolism.

Metyrapone, a pyridine derivative, primarily inhibits 11β-hydroxylase, and to a lesser degree, 17α-, 18-, and 19-hydroxylase activity. Oral metyrapone 750 to 6000 mg/day (administered before or with pituitary irradiation for a median of 27 months) achieved adequate control of hypercortisolaemia in 83% of 24 patients with Cushing's disease. Of the 6 patients who received only metyrapone, 3 had a relapse during 1 year of therapy. Reduction of cortisol levels was associated with clinical and biochemical improvement. Significant adverse effects included hirsutism, hypertension and transient hypoadrenalism.[41]

Aminoglutethimide inhibits the side-chain cleavage complex, the 21-, 17-, 11-, and 18-hydroxylases, aromatase, and C17-20 lyase enzymes. At 0.75 to 2.0 g/day orally, it was effective in relieving symptoms and signs of adrenocorticoid excess, in 42% of patients with Cushing's disease as preoperative therapy. Adverse reactions were dose dependent and included sedation, transient rash, nausea, anorexia, and thyroid function abnormalities.[42] Because high ACTH levels can overcome steroid synthesis blockade, aminoglutethimide can be given with metyrapone to obtain better results.

Trilostane, a carbonitrile derivative, inhibits the conversion of pregnenolone to progesterone. At 0.2 to 1.0 g/day orally, it has not had significant efficacy in the normalisation of hypercortisolism in patients with Cushing's disease.[37]

1.3.2 Neuromodulators

Valproic acid, a γ-aminobutyric acid (GABA)-reuptake inhibitor, may enhance GABA inhibition of hypothalamic corticorelin (CRH) release thereby lowering ACTH levels. Although some reports showed response to valproic acid, placebo-controlled studies were not able to demonstrate clinical or biochemical improvement in patients with Cushing's disease.[37,43] Some patients with Nelson's syndrome have responded to valproic acid 600 mg/day, with reductions in ACTH levels and tumour size.[44]

Bromocriptine was postulated to be effective in Cushing's disease resulting from intermediate lobe adenomas. Although dosages up to 30 mg/day appear to be ineffective, 1 study suggested that bromocriptine dosages >35 mg/day could attain a favourable clinical response and normal cortisol secretion.[45] Bromocriptine showed the greatest acute effect in suppressing ACTH secretion in a study in patients with Nelson's syndrome,[46] but reduction in ACTH levels during long term treatment is achieved only in a minority of patients.

Cyproheptadine, a serotonin antagonist, may suppress ACTH levels by acting at hypothalamic and pituitary levels. Although several cases of complete remission of Cushing's disease with cyproheptadine have been published, other case reports have not confirmed this. At least 24 mg/day were necessary to achieve response.[37] Cyproheptadine is generally ineffective in the treatment of Nelson's syndrome.[46,47]

Octreotide is not effective in decreasing ACTH levels in patients with Cushing's disease, although long term studies have not been performed.[37] The drug may decrease ACTH levels and improve visual field defects in patients with Nelson's syndrome, but changes in tumour size do not occur.[48]

1.3.3 Glucocorticoid-Receptor Antagonists

Mifepristone (RU-486), a progesterone and glucocorticoid receptor antagonist, has been useful in some patients with Cushing's syndrome resulting from ectopic ACTH secretion or adrenal cancer. However, the drug can increase ACTH and cortisol levels in patients with Cushing's disease, with possible subsequent loss of action. In addition, titration of mifepristone dosages may be problematic.[49]

1.4 Thyrotropin-Secreting Adenomas

Fewer than 1% of all pituitary adenomas are thyrotropin (TSH)-secreting tumours. Of these, 70% are macroadenomas. Symptoms include those of the pituitary mass and hyperthyroidism with goiter. Free liothyronine (tricodo thyronine;T_3) and thyroxine (T_4) are elevated but TSH is high or 'inappropriately' normal. The thyrotropin-releasing hormone (TRH; protirelin) test, α-subunit and α-subunit/TSH ratio measurements, and magnetic resonance imaging of the pituitary differentiate this entity from resistance to thyroid hormone syndrome. In atypical cases, the octreotide and T_3 suppression tests may be useful.[50]

The primary goal of treatment (fig. 4) is to remove or debulk the tumour mass by transsphenoidal or subfrontal surgery. If the tumour is unresectable or the surgery is contraindicated, the objective is to improve pituitary and thyroid function and decrease cell replication. Two thirds of the patients who undergo surgery and/or radiation therapy have normalisation of thyroid function tests, but only one third are cured.[51] When thionamides or radioiodine are used to control hyperthyroidism, a loss of feedback inhibition on TSH secreting tumour cells may occur. Thus, acceleration in tumour growth, increase in TSH secretion, and further goiter enlargement might be seen.

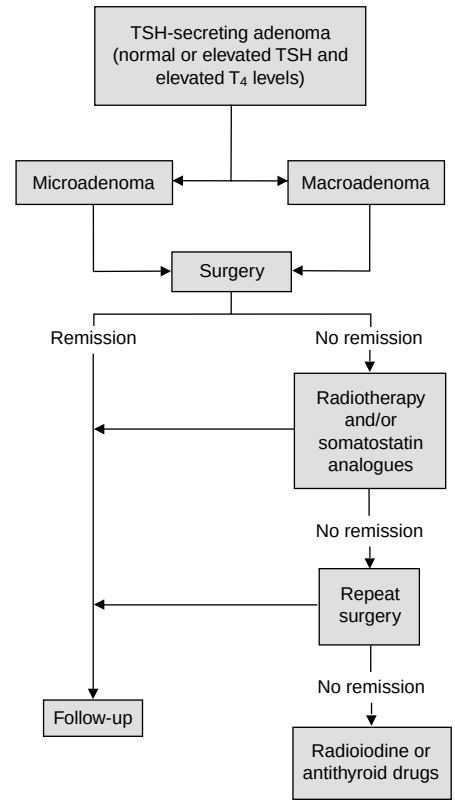

Fig. 4. Proposed treatment strategy for TSH-secreting adenomas.
Remission: normalisation of thyroid function tests and of TSH response to TRH. **T_4** = thyroxine; **TRH** = thyrotropin-releasing hormone, protirelin; **TSH** = thyrotropin.

1.4.1 Somatostatin Analogues

Somatostatin is a physiological inhibitor of TSH. Thus, somatostatin analogues are used for the treatment of TSH-secreting adenomas. Octreotide (50 to 750μg subcutaneously every 8 to 12 hours) can normalise TSH levels and restore the euthyroid state in 79% of patients, and improve visual field defects in 75% of patients. Shrinkage of adenoma and goiter volume also occurs in 52 and 18% of patients, respectively. 4% of patients have been resistant to octreotide in long term studies. Some patients develop hypothyroidism and require concomitant thyroid replacement therapy. Thus, octreotide can be used in patients with TSH-secreting adenomas who have not responded to surgery or radiotherapy.[50-53]

Lanreotide (30mg intramuscular injection every 10 to 15 days for 3 to 6 months) decreased TSH and normalised free T_3 and free T_4 levels but had no effects on tumour size in patients with TSH-secreting pituitary tumours. This medication was well tolerated.[54]

1.4.2 Dopamine Agonists

Dopamine agonists have been not consistently effective in the treatment of TSH-secreting tumours.[50,51]

1.5 Gonadotropin-Secreting Adenomas

Approximately 25% of pituitary tumours are classified as nonfunctioning or nonsecretory adenomas because, in general, they do not cause specific clinical syndromes of hormonal hypersecre-

tion. When studied *in vitro*, however, the great majority synthesise and/or secrete intact follicle-stimulating hormone (FSH) and luteinising hormone (LH) or free - and - subunits. This indicates that the majority of them are gonadotropin-secreting adenomas. Men and postmenopausal women usually present with symptoms of mass effect or hypopituitarism (hypogonadism).

Resection or debulking of the tumour by transsphenoidal surgery is the treatment of choice for gonadotropin-secreting adenomas. 70 to 80% of patients with visual field defects experience improvement, but 15% of tumours recur within 5 years after successful surgery. In patients with postsurgical residual adenoma, pituitary irradiation can be used to prevent regrowth and even decrease the size of the remnant tumour. In the interim, some medications may be useful.[1] For a proposed strategy of the treatment of gonadotropin-secreting adenomas, see figure 5.

1.5.1 Dopamine Agonists

Bromocriptine is usually not beneficial for the treatment of gonadotropin-secreting adenomas. Occasional reports have shown reductions in serum levels of FSH, LH and α-subunit, and improvements in the visual defect abnormalities, without changes in tumour size.[55,56]

1.5.2 Somatostatin Analogues

Several studies have shown that octreotide does not effectively reduce tumour size, decrease gonadotropin levels or improve visual function in the majority of patients with gonadotropin-secreting adenomas. However, a recent report showed amelioration in visual abnormalities in 40% of patients after 2 months of therapy with octreotide; shrinkage of the adenoma was reported in 3 of 7 patients.[57]

1.5.3 Gonadotropin-Releasing Hormone (GnRH) Agonists

Long-acting gonadotropin-releasing hormone (GnRH) agonists that down-regulate gonadotropin secretion in healthy individuals are not consistently successful in improving serum gonadotropin levels or reducing the size of the adenoma in patients with gonadotropin-secreting pituitary tumours. Conversely, they may increase serum levels of α-subunit.[58]

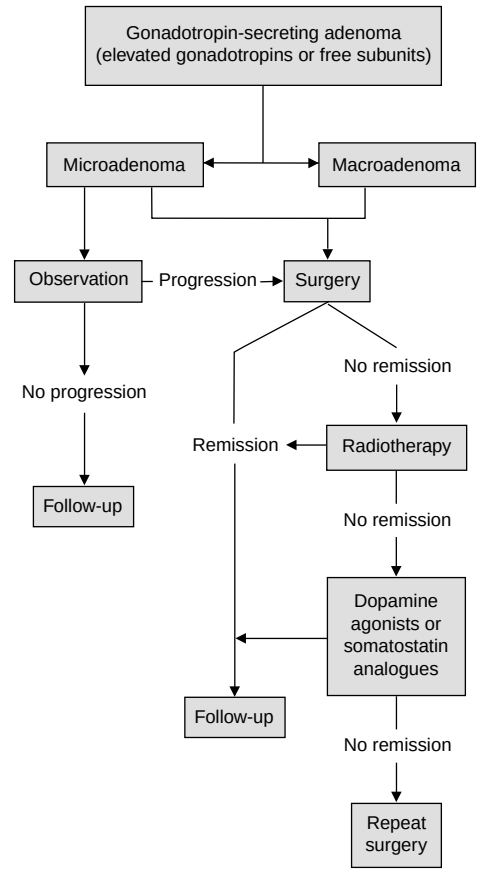

Fig. 5. Proposed treatment strategy for gonadotropin-secreting adenomas.
Remission: Removal of tumour mass and improvement in hormonal hypersecretion (when present).

1.5.4 GnRH Antagonists

The GnRH antagonist Nal-Glu (5mg subcutaneously twice daily) normalised or suppressed gonadotropin levels in patients with FSH-secreting pituitary adenomas without reducing tumour size.[59] These findings suggest that the secretion of FSH, but not the growth of the tumour, is dependent on endogenous GnRH.

2. Hypopituitarism

Pituitary insufficiency is the partial or complete loss of the anterior hypophyseal function caused by hypothalamic or pituitary disease. The classic sequence of loss of pituitary secretion is GH, LH/

FSH, TSH, and ACTH, with GH being the most common deficiency. There are 8 to 10 new cases of hypopituitarism per million adults every year.[60] Pituitary tumours account for more than 95% of cases of pituitary insufficiency, with macroadenomas being the most frequent cause. Clinical manifestations of hypopituitarism are diverse and depend on the extent and severity of the hypophyseal dysfunction. The diagnosis of a complete loss of function is simple, but dynamic tests are often necessary to discover partial deficiencies. Once the cause of the hypopituitarism is clear, replacement therapy of the deficient hormone(s) is the goal.[61] Cortisol, thyroxine, sex hormones, and if necessary, GH, should be replaced in that order.

2.1 Prolactin Deficiency

Although hyperprolactinaemia is more commonly associated with pituitary insufficiency than is hypoprolactinaemia, failure of lactation is often the earliest clue to panhypopituitarism resulting from Sheehan's syndrome (pituitary necrosis during the peripartum period). There is no specific therapy for hypoprolactinaemia.

2.2 GH Deficiency

Adult onset GH deficiency (partial or total) can cause alterations in body composition (reduced lean body mass and increased centrally distributed fat mass), physical performance, psychological well-being and quality of life, as well as osteoporosis. GH deficiency has also been implicated in reduced life expectancy (due to increased mortality from cardiovascular disease).[62] Adult onset GH deficiency may result from hypothalamic or pituitary damage brought about by tumours, radiation therapy, etc. Patients with childhood onset GH deficiency should be retested as adults before committing them to GH replacement therapy.[63]

All patients with severe GH deficiency are eligible for GH replacement. Severe GH deficiency is defined as a peak GH level <3 μg/L in response to hypoglycaemia, using polyclonal competitive radioimmunoassays. Patients should be on replacement therapy for other hormonal deficits before testing. If an adult has other pituitary hormone deficiencies, only one abnormal GH provocative test is necessary. In adults with suspected isolated GH deficiency, a second abnormal biochemical test of GH status is required to confirm the diagnosis.[63]

The goal of the treatment of GH deficiency is to correct the abnormalities associated with GH deficiency and to keep IGF-I levels in the age-related normal range. GH replacement therapy should be initiated at a dosage of 0.15 to 0.30 mg/day (to convert mg to IU multiply by 3) given as a subcutaneous injection each evening. The dosage is gradually increased (by 0.15 mg/day at monthly intervals) to reach the maintenance dosage, which seldom is greater than 1.0 mg/day. If a patient perceives no benefit after 6 months, GH can be discontinued. Otherwise, GH can be continued for life. Adverse effects are transient and dosage dependent. They include oedema, carpal tunnel syndrome, paresthesias, arthralgias, and glucose intolerance. Contraindications are active malignancy, proliferative diabetic retinopathy and benign intracranial hypertension. Although early pregnancy is not a contraindication, GH replacement therapy should be discontinued in the second trimester as GH is synthesised by the placenta.[63-65]

GH secretagogues or GH-releasing peptides are synthetic, non-natural peptidyl and nonpeptidyl molecules, which act at both the pituitary and hypothalamic level via a specific receptor that is different from the GHRH receptor. They are potent stimulators of GH secretion that can be administered via subcutaneous, intravenous, oral or intranasal routes. Because these agents require the integrity of the hypothalamo-pituitary axis, patients with adult-onset GH deficiency who have organic hypopituitarism do not benefit from them. However, these agents may have a role in children with short stature due to GH deficiency.[66,67]

The actual benefits of GH replacement therapy in adults are still uncertain. Most importantly, an improvement in the morbidity and mortality rates in hypopituitary adults during GH replacement therapy has never been documented. Obviously, more studies are needed to justify GH administration as a necessary part of replacement therapy in adults with pituitary insufficiency.

2.3 Gonadotropin Deficiency

Men with hypogonadotropic hypogonadism have low or 'inappropriately' normal LH and FSH levels and low testosterone levels. Manifestations include loss of normal sexual function, loss of bone and muscle mass, and a decline in general health.[68] The aim of treatment is to induce or maintain secondary sexual characteristics, sexual behaviour and male habitus. If fertility is not desired, the treatment of choice is testosterone-replacement therapy. Several forms of testosterone delivery are available: testosterone enanthate or cipionate (200 or 300mg given intramuscularly every 2 or 3 weeks, respectively) and the testosterone transdermal (TTD) system are the usual methods of therapy.[69,70] Intramuscular testosterone enanthate or cipionate dosages and administration intervals can be adjusted according to clinical response. The TTD system maintains stable hormone levels over a long period of time but is 10 to 20 times more expensive than the injections.

The TTD system includes scrotal (4 to 6 mg/day) and nonscrotal (2.5 to 5.0 mg/day) patches. The principal adverse effects of these formulations are local reactions (pruritus, burn-like blisters, erythema, and vesicles) which result in treatment withdrawal in 10% of patients.[71] Prostate-specific antigen and hematocrit should be checked before and after starting testosterone-replacement therapy.

Several second line and experimental modalities of therapy have also been used for the treatment of hypogonadal men. For example, testosterone undecanoate (40mg orally 3 or 4 times daily) is a 17α-hydroxyl ester which has been shown to cause variable clinical response in men.[72] Also, subcutaneous implanted pellets of fused crystalline testosterone (6 x 100mg or 3 x 200mg) provided normal circulating testosterone levels for 4 to 5 months.[73] Other studies in hypogonadal men showed that the second-generation long-acting testosterone microcapsule formulation (630mg in dextran solution) provided eugonadal levels of testosterone for up to 11 weeks[74] and the long-acting testosterone ester, testosterone bucyclate (600mg intramuscular injection), normalised androgen levels for 3 months.[75] Finally, a rapidly absorbed sublingual formulation of cyclodextrin-complexed testosterone has also been used.[76]

Women with hypogonadotropic hypogonadism may have oligo/amenorrhoea, hot flashes/flushes, dyspareunia, loss of libido, infertility, breast atrophy, osteoporosis, and premature cardiovascular disease. Treatment should correct the hypoestrogenaemia resulting from low or 'inappropriately' normal FSH or LH levels. In premenopausal women, who do not desire pregnancy, a combined oral contraceptive (with 20 to 35μg of ethinylestradiol) is indicated.[60] In postmenopausal women with an intact uterus, estrogens and progestagens are given cyclically or continuously. One such cyclic regimen consists of conjugated estrogens at 0.625 to 1.25 mg/day for 25 days with medroxyprogesterone acetate at 5 to 10 mg/day for the last 10 to 14 days. If the uterus has been removed, estrogens are administered continuously. Other estrogen formulations (patches, percutaneous and implants) and hormone replacement combinations tablets are also available.[77]

If fertility is desired, therapy with human chorionic gonadotropin (hCG; a LH-like hormone) and human menopausal gonadotropin or menotropins (a mix of LH and FSH) can be used.[78,79] Recently, gonadotropins have been produced by recombinant DNA technology, replacing hCG and menotropins as first line of therapy.[80] Several dosages and frequencies of administration have been suggested. Restoration of spermatogenesis in men requires the following sequence: hCG is administered first, to activate testicular testosterone production by the Leydig cells. When testosterone levels have been maintained in the normal range for 2 to 3 months, FSH is added to stimulate spermatogenesis. Often, this requires 6 to 12 months. In women, the sequence is reversed: FSH is given first, to induce follicular maturation, and then a single bolus of LH is given to induce ovulation. Ovarian ultrasound and rapid estrogen assay are monitored to avoid multiple ovulation. Unfortunately, multiple pregnancies will develop in more than 25% of patients.[79]

2.4 Corticotropin Deficiency

Tiredness, fatigue, anorexia, nausea, vomiting, diarrhoea, weight loss, and postural hypotension

characterise secondary adrenal insufficiency. Because patients with mild or recent onset secondary adrenal failure may have a normal ACTH stimulation test, the insulin tolerance test is the preferred method of evaluation for these patients.[81] The goal of replacement therapy is to administer the minimum dosage of glucocorticoids that improve the symptoms, avoiding overtreatment (Cushingoid features and osteoporosis) and undertreatment (residual symptoms).[82] The starting dosage of hydrocortisone is 10 to 12 mg/m^2/day, which is about 20 mg/ day for normal adults. Although the usual form of administration is to give 15mg upon wakening and 5mg at 5pm, recent evidence suggests that 10mg/ 5mg/5mg (awakening/lunch/dinner) is more physiological and patients feel better.[83] Fatigue and early morning headache may indicate overnight hypocortisolism.[84] Dosages can be evaluated clinically, although measuring serum and urinary cortisol levels may be required occasionally to verify sufficiency of replacement.

For patients undergoing surgery, the dosage has to be increased depending on the extent of the procedure. In general, for minor, moderate, and major interventions, additional daily supplements of 25mg, 50 to 75mg, and 100 to 150mg, respectively, are required for 48 to 72 hours. They are given as intravenous infusions or boluses every 6 to 8 hours.[85] A similar approach is necessary in patients with trauma, infections or other severe illnesses.[86] Other glucocorticoids may be used instead of hydrocortisone. Cortisone (25mg in the morning and 12.5mg in the afternoon) or prednisone (5mg in the morning) are acceptable alternatives. The dosages of these medications need to be increased during stressful illnesses in the same proportion as hydrocortisone. Unlike patients with primary adrenal insufficiency, patients with ACTH deficiency do not need mineralocorticoids as part of the therapy.

2.5 Thyrotropin Deficiency

Secondary hypothyroidism is characterised by slowing of mental functions, cold intolerance, fatigue, dry skin, constipation and sleepiness. Unlike primary hypothyroidism, symptoms such as periorbital oedema, hoarseness, weight gain and hypercholesterolaemia occur less frequently, and there is no goiter. Biochemical evaluation shows low T_4 and T_3 levels with low or 'inappropriately' normal TSH levels.[87] Thyroxine is the treatment of choice for central hypothyroidism. Before starting this therapy, concomitant adrenal insufficiency has to be ruled out in order to avoid precipitation of an adrenal crisis. In young or noncardiac patients, thyroxine can be started at 0.1 to 0.15 mg/day, given in the morning. In patients over 60 years of age or with ischaemic cardiac disease, thyroxine should be started at 0.025 to 0.05 mg/day and subsequently raised by 0.025 to 0.05 mg/day every 3 to 4 weeks, if tolerated.[88] The adequacy of the dosage is evaluated according to the normalisation of the clinical manifestations and serum levels of total or free T_4 levels. Adverse effects are minimal, but overtreated patients with high levels of serum T_4 may have higher risks of developing osteoporosis and atrial fibrillation in the long term.

3. Conclusion

Pituitary diseases are relatively common in the general population. Pituitary adenomas have different manifestations depending on tumour size, gender and age. The goal of treatment is to improve mass effect, hormonal hyper- or hyposecretion, and to prevent recurrence. Transsphenoidal surgery is the treatment of choice for all pituitary tumours with the exception of prolactinomas. Thus, pituitary irradiation and medical therapy are adjuvant to the surgical approach. A proposed treatment strategy for the different pituitary adenomas is given in figures 1 to 5. The goal of the treatment of hypopituitarism is to achieve clinical and biochemical improvement. In general, hormonal replacement therapy is a lifelong commitment.

References

1. Shimon I, Melmed S. Management of pituitary tumors. Ann Intern Med 1998; 129 (6): 472-83
2. Corenblum B, Donovan L. The safety of physiological estrogen plus progestin replacement therapy with oral contraceptive therapy in women with pathological hyperprolactinemia. Fertil Steril 1993; 59: 671-4
3. Molitch ME, Thorner MO, Wilson C. Management of prolactinomas. J Clin Endocrinol Metab 1997; 82: 996-1000
4. Molitch ME, Elton RL, Blackwell RE, et al. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. J Clin Endocrinol Metab 1985; 60: 698-705

5. Liuzzi A, Dallabonzana D, Oppizzi G, et al. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. N Engl J Med 1985; 313 (11): 656-9
6. Katz E, Schran HF, Adashi EY. Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. Obstet Gynecol 1989; 73 (3): 517-9
7. Schettini G, Lombardi G, Merola B, et al. Rapid and long-lasting suppression of prolactin secretion and shrinkage of prolactinomas after injection of long-acting repeatable form of bromocriptine (parlodel LAR). Clin Endocrinol 1990; 33: 161-9
8. Pellegrini I, Rasolonjanahary R, Gunz G, et al. Resistance to bromocriptine in prolactinomas. J Clin Endocrinol Metab 1989; 69: 500-9
9. Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 1994; 331 (14): 904-9
10. Molitch ME. Medical treatment of prolactinomas. Endocrinol Metab Clin North Am 1999 Mar; 28 (1): 143-69
11. Colao A, Di Sarno A, Sarnacchiaro F, et al. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 1997; 82: 876-83
12. Kleinberg DL, Boyd III AE, Wardlaw S, et al. Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. N Engl J Med 1983; 309 (12): 704-9
13. Chiodini P, Liuzzi A, Cozzi R, et al. Size reduction of macroprolactinomas by bromocriptine or lisuride treatment. J Clin Endocrinol Metab 1981; 53: 737-43
14. Vance ML, Lipper M, Klibanski A, et al. Treatment of prolactin-secreting pituitary macroadenomas with the long-acting non-ergot dopamine agonist CV 205-502. Ann Intern Med 1990; 112 (9): 668-73
15. Ciccarelli E, Camanni F. Diagnosis and drug therapy of prolactinomas. Drugs 1996; 51 (6): 954-65
16. Shimon I, Yan X, Taylor JE, et al. Somatostatin receptor (SSTR) subtype-selective analogues differentially suppress in vitro growth hormone and prolactin in human pituitary adenomas. J Clin Invest 1997; 100 (9): 2386-92
17. Melmed S, Jackson I, Kleinberg D, et al. Current treatment guidelines for acromegaly. J Clin Endocrinol Metab 1998; 83: 2646-52
18. Barkan AL, Halasz I, Dornfeld KJ, et al. Pituitary irradiation is ineffective in normalizing plasma insulin-like growth factor I in patients with acromegaly. J Clin Endocrinol Metab 1997; 82: 3187-91
19. Vance ML, Harris AG. Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide. Arch Intern Med 1991; 151: 1573-8
20. Ezzat S, Snyder PJ, Young WF, et al. Octreotide treatment of acromegaly: a randomized multicenter study. Ann Intern Med 1992; 117 (9): 711-8
21. Newman CB, Melmed S, Snyder PJ, 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. J Clin Endocrinol Metab 1995; 80: 2768-75
22. Tauber JP, Babin TH, Tauber MT, et al. Long-term effects of continuous subcutaneous infusion of the somatostatin analog octreotide in the treatment of acromegaly. J Clin Endocrinol Metab 1989; 68: 917-24
23. Stewart PM, Kane KF, Stewart SE, et al. Depot long-acting somatostatin analog (sandostatin-LAR) is an effective treatment for acromegaly. J Clin Endocrinol Metab 1995; 80: 3267-72
24. Davies PH, Stewart SE, Lancranjan I, et al. Long-term therapy with long-acting octreotide (sandostatin-LAR) for the management of acromegaly. Clin Endocrinol 1998; 48: 311-6
25. Caron P, Morange-Ramos I, Cogne M, et al. Three year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide. J Clin Endocrinol Metab 1997; 82: 18-22
26. Jaffe CA, Barkan AL. Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin North Am 1992 Sep; 21 (3): 713-35
27. Abs R, Verhelst J, Maiter D, et al. Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab 1998; 83: 374-8
28. Colao A, Ferone D, Marzullo P, et al. Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab 1997; 82: 518-23
29. Lombardi G, Colao A, Ferone D, et al. CV 205-502 treatment in therapy-resistant acromegalic patients. Eur J Endocrinol 1995; 132: 559-64
30. Fløgstad AK, Halse J, Grass P, et al. A comparison of octreotide, bromocriptine, or a combination of both drugs in acromegaly. J Clin Endocrinol Metab 1994; 79: 461-5
31. Chen WY, Chen N, Yun J, et al. In vitro and in vivo studies of antagonistic effects of human growth hormone analogs. J Biol Chem 1994 Feb; 269 (22): 15892-7
32. Van der Lely AJ, Lamberts SWJ, Barkan AL, et al. A six week, double blind, placebo controlled study of a growth hormone antagonist, B2036-PEG (trovert™), in acromegalic patients [[abstract no. OR4-1]. In: The 80th Annual Meeting of the Endocrine Society: New Orleans, 1998
33. Jaffe CA, DeMott-Friberg R, Barkan AL. Suppression of growth hormone (GH) secretion by a selective GH-releasing hormone (GHRH) antagonist. J Clin Invest 1993; 92: 695-701
34. Jaffe CA, DeMott-Friberg R, Frohman LA, et al. Suppression of growth hormone (GH) hypersecretion due to ectopic GH-releasing hormone (GHRH) by a selective GHRH antagonist. J Clin Endocrinol Metab 1997; 82: 634-7
35. Orth DN. Cushing's syndrome. N Engl J Med 1995; 332: 791-803
36. Estrada J, Boronat M, Mielgo M, et al. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med 1997; 336: 215-9
37. Miller JW, Crapo L. The medical treatment of Cushing's syndrome. Endocr Rev 1993; 14 (4): 443-58
38. Invitti C, Giraldi FP, De Martin M, et al. Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. J Clin Endocrinol Metab 1999; 84: 440-8
39. Luton JP, Mahoudeau JA, Bouchard P, et al. Treatment of Cushing's disease by O,P'DDD: survey of 62 cases. N Engl J Med 1979; 300: 459-64
40. Schulte HM, Benker G, Reinwein D, et al. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. J Clin Endocrinol Metab 1990; 70: 1426-30
41. Verhelst JA, Trainer PJ, Howlett TA, et al. Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinol 1991; 35: 169-78
42. Misbin RI, Canary J, Willard D. Aminoglutethimide in the treatment of Cushing's syndrome. J Clin Pharmacol 1976; 16 (11-12): 645-51
43. Beckers A, Stevenaert A, Pirens G, et al. Cyclical Cushing's disease and its successful control under sodium valproate. J Endocrinol Invest 1990; 13: 923-9
44. Loli P, Berselli ME, Vignati F, et al. Size reduction of an ACTH-secreting pituitary macroadenoma in Nelson's syndrome by sodium valproate: effect of withdrawal and re-institution of treatment. Acta Endocrinol (Copenh) 1988; 119: 435-42
45. Mercado-Asis LB, Yasuda K, Murayama M, et al. Beneficial effects of high daily dose bromocriptine treatment in Cushing's disease. Endocrinol Jpn 1992; 39 (4): 385-95

46. Mercado-Asis LB, Yanovski JA, Tracer HL, et al. Acute effects of bromocriptine, cyproheptadine, and valproic acid on plasma adrenocorticotropin secretion in Nelson's syndrome. J Clin Endocrinol Metab 1997; 82: 514-7
47. Cassar J, Mashiter K, Joplin GF, et al. Cyproheptadine in Nelson's syndrome [[letter]. Lancet 1976; 2: 426
48. Petrini L, Gasperi M, Pilosu R, et al. Long-term treatment of Nelson's syndrome by octreotide: a case report. J Endocrinol Invest 1994; 17: 135-9
49. Sartor O, Cutler GB. Mifepristone: treatment of Cushing's syndrome. Clin Obstet Gynecol 1996; 39 (2): 506-10
50. Brucker-Davis F, Oldfield EH, Skarulis MC, et al. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab 1999; 84: 476-86
51. Beck-Peccoz P, Brucker-Davies F, Persani L, et al. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996; 17: 610-38
52. Comi RJ, Gesundheit N, Murray L, et al. Response of thyrotropin-secreting pituitary adenomas to a long-acting somatostatin analogue. N Engl J Med 1987; 317: 12-7
53. Chanson P, Weintraub BD, Harris AG. Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas. Ann Intern Med 1993; 119: 236-40
54. Gancel A, Vuillermet P, Legrand A, et al. Effects of a slow-release formulation of the new somatostatin analogue lanreotide in TSH-secreting pituitary adenomas. Clin Endocrinol 1994; 40: 421-8
55. Berezin M, Olchovsky D, Pines A, et al. Reduction of follicle-stimulating hormone (FSH) secretion in FSH-producing pituitary adenoma by bromocriptine. J Clin Endocrinol Metab 1984; 59: 1220-3
56. Vance ML, Ridgway EC, Thorner MO. Follicle-stimulating hormone- and -subunit-secreting pituitary tumor treated with bromocriptine. J Clin Endocrinol Metab 1985; 61: 580-4
57. Warnet A, Harris AG, Renard E, et al. A prospective multicenter trial of octreotide in 24 patients with visual defects caused by nonfunctioning and gonadotropin-secreting pituitary adenomas. Neurosurgery 1997; 41: 786-97
58. Sassolas G, Lejeune H, Trouillas J, et al. Gonadotropin-releasing hormone agonists are unsuccessful in reducing tumoral gonadotropin secretion in to patients with gonadotropin-secreting pituitary tumors. J Clin Endocrinol Metab 1988; 67: 180-5
59. McGrath GA, Goncalves RJ, Udupa JK, et al. New technique for quantitation of pituitary adenoma size: use in evaluating treatment of gonadotroph adenomas with a gonadotropin-releasing hormone antagonist. J Clin Endocrinol Metab 1993; 76: 1363-8
60. Lamberts SWJ, De Herder WW, Van der Lely AJ. Pituitary insufficiency. Lancet 1998; 352: 127-34
61. Vance ML. Hypopituitarism. N Engl J Med 1994; 330: 1651-62
62. Carroll PV, Christ ER and the members of Growth Hormone Research Society Scientific Committee. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. J Clin Endocrinol Metab 1998; 83: 382-94
63. Summary statement of the Growth Hormone Research Society Workshop on adult growth hormone deficiency. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency. J Clin Endocrinol Metab 1998; 83: 379-81
64. Al-Shoumer KAS, Page B, Thomas E, et al. Effects of four years' treatment with biosynthetic human growth hormone (GH) on body composition in GH-deficient hypopituitary adults. Eur J Endocrinol 1996; 135: 559-67
65. De Boer H, Van der Veen E. Guidelines for optimizing growth hormone replacement therapy in adults. Horm Res 1997; 48 (5 Suppl.): 21-30
66. Argente J, Garcia-Segura LM, Pozo J, et al. Growth hormone-releasing peptides: clinical and basic aspects. Horm Res 1996; 46: 155-9
67. Ghigo E, Arvat E, Camanni F. Orally active growth hormone secretagogues: state of the art and clinical perspectives. Ann Med 1998; 30: 159-68
68. Plymate S. Hypogonadism. Endocrinol Clin North Am 1994 Dec; 23 (4): 749-72
69. Bhasin S, Bremner WJ. Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab 1997; 82: 3-8
70. Bagatell CJ, Bremner WJ. Androgens in men: uses and abuses. N Engl J Med 1996; 334: 707-14
71. McClellan KJ, Goa KL. Transdermal testosterone. Drugs 1998 Feb; 55 (2): 253-8
72. Gooren LJ. A ten-year safety study of the oral androgen testosterone undecanoate. J Androl 1994; 15: 212-5
73. Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. J Clin Endocrinol Metab 1990; 71: 216-22
74. Bhasin S, Swerdloff RS, Steiner B, et al. A biodegradable testosterone microcapsule formulation provides uniform eugonadal levels of testosterone for 10-11 weeks in hypogonadal men. J Clin Endocrinol Metab 1992; 74: 75-83
75. Behre HM, Nieschlag E. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. J Clin Endocrinol Metab 1992; 75: 1204-10
76. Salehian B, Wang C, Alexander G, et al. Pharmacokinetics, bioefficacy, and safety of sublingual testosterone cyclodextrin in hypogonadal men: comparison to testosterone enanthate. J Clin Endocrinol Metab 1995; 80: 3567-75
77. McKinney KA, Thompson W. A practical guide to prescribing hormone replacement therapy. Drugs 1998 Jul; 56 (1): 49-57
78. Burris AS, Rodbard HW, Winters SJ, et al. Gonadotropin therapy in men with isolated hypogonadotropic hypogonadism: the response to human chorionic gonadotropin is predicted by initial testicular size. J Clin Endocrinol Metab 1988; 66: 1144-51
79. Baird DT. Amenorrhoea. Lancet 1997; 350: 275-9
80. Loumaye E, Campbell R, Salat-Baroux J. Human follicle-stimulating hormone produced by recombinant DNA technology: a review for clinicians. Hum Reprod Update 1995; 1 (2): 188-99
81. Oelkers W. Adrenal insufficiency. N Engl J Med 1996; 335: 1206-12
82. Peacey SR, Guo CY, Robinson AM, et al. Glucocorticoid replacement therapy: are patients over treated and does it matter? Clin Endocrinol 1997; 46: 255-61
83. Howlett TA. An assessment of optimal hydrocortisone replacement therapy. Clin Endocrinol 1997; 46: 262-8
84. Al-Shoumer KAS, Ali K, Anyaoku V, et al. Overnight metabolic fuel deficiency in patients treated conventionally for hypopituitarism. Clin Endocrinol 1996; 45: 171-8
85. Salem M, Tainsh RE, Bromberg J, et al. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. Ann Surg 1994; 219 (4): 416-25
86. Lamberts SWJ, Bruining HA, De Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997; 337: 1285-92
87. Lindsay RS. Hypothyroidism. Lancet 1997; 349: 413-7
88. Toft AD. Thyroxine therapy. N Engl J Med 1994; 331: 174-80

Correspondence and offprints: Dr *A.L. Barkan*, Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan, 48109-0354, USA.
E-mail: abarkan@umich.edu