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# Chapter e98: Pituitary Gland Disorders

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## KEY CONCEPTS

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1. Pharmacologic therapy for acromegaly should be considered when surgery and irradiation are contraindicated, when there is a poor likelihood of surgical success, when rapid control of symptoms is needed, or when other treatments have failed to normalize growth hormone (GH) and insulin-like growth factor-1 (IGF-1) serum concentrations.

2. Pharmacotherapy for acromegaly using dopamine agonists has several advantages including oral administration and lower cost when compared to somatostatin analogs and pegvisomant. However, dopamine agonists effectively normalize IGF-1 serum concentrations in only 10% to 30% of patients. Therefore, somatostatin analogs remain the mainstay of therapy.

3. Blood glucose concentrations should be monitored frequently in the early stages of somatostatin analog therapy, especially when using pasireotide.

4. Pegvisomant appears to be the most effective agent for normalizing IGF-1 serum concentrations.

5. Recombinant growth hormone (GH) is currently considered the drug of choice for the treatment of children with growth hormone–deficient short stature. Prompt diagnosis of growth hormone deficiency (GHD) and initiation of replacement therapy with recombinant GH is crucial for optimizing final adult heights.

6. All GH products are equally effective. The recommended initial dose for treatment of GHD short stature in children is 0.16 to 0.24 mg/kg/wk.

7. Pharmacologic agents that antagonize dopamine or increase the release of prolactin can induce hyperprolactinemia. Discontinuation of the offending medication and initiation of an appropriate therapeutic alternative usually normalizes serum prolactin concentrations.

8. Cabergoline is more effective than bromocriptine for the medical management of prolactinomas and offers the advantage of less-frequent dosing and fewer adverse effects.

9. Although currently available data do not suggest that cabergoline has significant teratogenic potential, cabergoline is not recommended for use during pregnancy. Patients receiving cabergoline or bromocriptine who plan to become pregnant should discontinue the medication as soon as pregnancy is detected.

10. Pharmacologic treatment of panhypopituitarism includes the use of glucocorticoids, thyroid hormone, sex steroids, and recombinant GH, when appropriate, as lifelong replacement therapies.

## PATIENT CARE PROCESS

### Patient Care Process for Hyperprolactinemia

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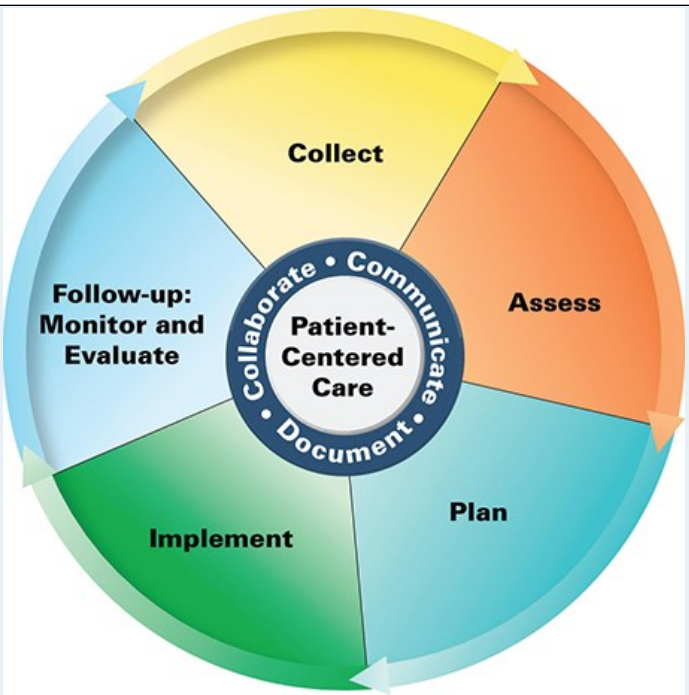


### Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient history (past medical, menstrual cycle, family medical history)
- Social history (stress level, physical activity, dietary habits)
- Current medications including prescription, non-prescription, and herbal products
- Objective data
- Labs (eg, prolactin, macroprolactin, serum β-HCG, FSH, TSH, free T4, AST, ALT, BUN, and SCr)
    - DXA T-score of the lumbar spine
    - MRI of the pituitary gland
    - Objective confirmation of signs (see Table e98-5)

### Assess

- Presence of symptoms related to local effects of prolactinoma (see Table e98-5)
- Presence of medications likely to impact prolactin levels (see Table e98-4)
- Emotional status (ie, presence of stress)
- Patient's desire to become pregnant in the future

### Plan*

- If drug-induced, discontinuation of offending medication and initiation of therapeutic alternative
- If not drug-induced, treat with a dopamine agonist, if appropriate

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- Consider sex hormone replacement therapy if clinically appropriate
- Monitoring parameters including efficacy (eg, prolactin, gonadal function, tumor size, galactorrhea) and safety (bromocriptine: central nervous system [CNS] and gastrointestinal [GI] adverse effects, cabergoline: CNS and GI adverse effects, blood pressure, and cardiac valvular function, if appropriate)
- Patient education (eg, the purpose of treatment, lifestyle modification, risks and benefits of invasive procedures, drug-specific side effects, medication administration techniques, discontinue treatment if pregnancy detected)
- Self-monitoring for regularity of menstrual cycle in women and libido in men
- Referrals to other providers when appropriate

**Implement***

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies (eg, dose chart or pillbox) to maximize adherence
- Schedule follow-up (eg, prolactin levels to titrate dosing, adherence assessment, side effect assessment, repeat imaging)

**Follow-Up: Monitor and Evaluate**

- Prolactin levels (initially monitor every 3-4 weeks and 6-12 months once normalized)
- Gonadal function, bone loss, tumor size, and visual defects
- Presence of medication-specific adverse effects
- Patient adherence to treatment plan using multiple sources of information
- Pregnancy status
- Reevaluate the role of dopamine agonist therapy after 2 years of treatment in the absence of visible tumor

****Collaborate with patient, caregivers, and other healthcare professionals.***

## BEYOND THE BOOK

**BEYOND THE BOOK**

Create a diagram of anterior pituitary hormones, noting the upstream signals (ie, hypothalamic-releasing or inhibiting hormones) and downstream targets of the hormones secreted by the anterior pituitary. When applicable, note inhibitory or excitatory feedback mechanisms in this process.

## INTRODUCTION

It wasn't until the 1950s that the physiologic importance of pituitary hormones was understood and the neurohormonal regulation of the pituitary by the hypothalamus described.[1] The pituitary gland plays an essential role in homeostasis, and for this reason, it is often referred to as the *master gland.* The hypothalamus and the pituitary gland are closely connected, and together they provide a means of communication between the brain and many of the body's endocrine organs. The hypothalamus uses input from the central nervous system and metabolic signals from the body to control the secretion of pituitary hormones that regulate growth, thyroid function, adrenal activity, reproduction, lactation, and fluid balance.

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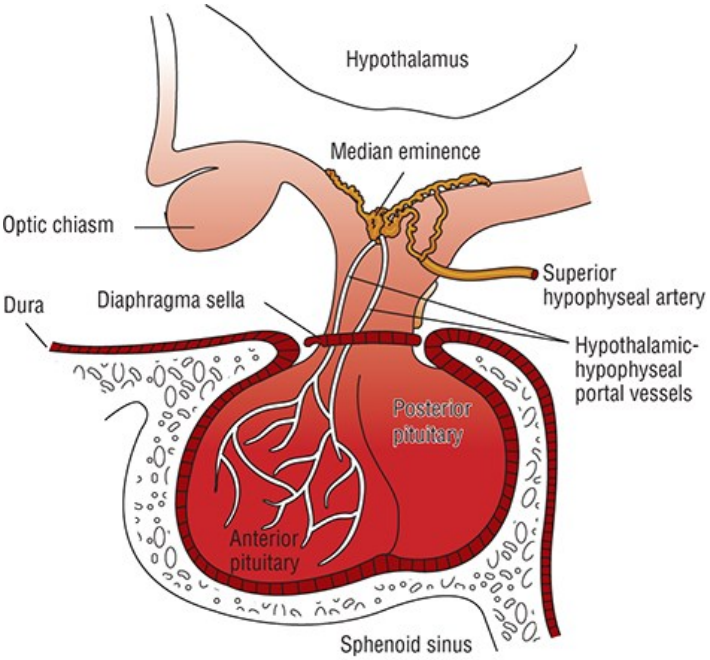
## ANATOMY AND PHYSIOLOGY

The hypothalamus (Fig. e98-1) is a small region at the base of the brain that receives autonomic nervous input from different areas of the body to regulate limbic functions, food and water intake, body temperature, cardiovascular function, respiratory function, and diurnal rhythms. In addition, the hypothalamus controls the release of hormones from the anterior and posterior regions of the pituitary gland. Neurons in the hypothalamus produce vasopressin and oxytocin and make many hormone-releasing factors that stimulate or inhibit the release of trophic hormones from the anterior pituitary that subsequently stimulate endocrine tissues to grow and release hormones. At the base of the hypothalamus, a projection known as the *median eminence* is rich with nerve axons and blood vessels and provides both chemical and physical connections between the hypothalamus and the pituitary gland.

**FIGURE e98-1**

Pituitary gland.

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The pituitary gland, also referred to as the *hypophysis*, is located at the base of the brain in a cavity of the sphenoid bone known as the *sella turcica*. The pituitary is separated from the brain by an extension of the dura mater known as the *diaphragma sellae*. The pituitary is a very small gland, weighing between 0.4 and 1 g in adults. It is divided into two distinct regions: the anterior lobe, or adenohypophysis, and the posterior lobe, or the neurohypophysis (see Fig. e98-1).

The posterior pituitary gland secretes two major hormones: oxytocin and vasopressin (antidiuretic hormone) (Table e98-1). Oxytocin release from the posterior pituitary causes contraction of the smooth muscles in the breast during lactation. It also plays a role in uterine contraction during parturition. Vasopressin is essential for proper fluid balance and acts on the renal collecting ducts to conserve water. Oxytocin and vasopressin are synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. The posterior pituitary gland contains the terminal nerve endings of these two nuclei as well as specialized secretory granules that release hormones in response to appropriate signals. Loss of anterior pituitary function does not typically affect the release of vasopressin or oxytocin because these hormones are synthesized in the hypothalamus.

TABLE e98-1

**Pituitary Hormones**

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| Hormone | Stimulated by | Inhibited by | Physiologic Effects |
|---|---|---|---|
| **Posterior Pituitary Hormones** | | | |
| Vasopressin (ADH) | • Hyperosmolality<br>• Hypovolemia<br>• Volume depletion | • Hypervolemia<br>• Hypoosmolality | • Acts on renal collecting ducts to prevent diuresis<br>• Vasoconstriction |
| Oxytocin | • Parturition<br>• Suckling | | • Uterine contraction<br>• Milk ejection |
| **Anterior Pituitary Hormones** | | | |
| Growth Hormone (GH) | *Physiologic* | *Physiologic* | |
| | • GH-releasing hormone Ghrelin<br>• ADH<br>• GABA<br>• Norepinephrine<br>• Dopamine<br>• Serotonin<br>• Estrogen<br>• Sleep<br>• Stress<br>• Exercise | • Somatostatin<br>• Elevated IGF-1<br>• Growth hormone<br>• Progesterone<br>• Glucocorticoids<br>• Postprandial hyperglycemia<br>• Elevated free fatty acids | • Stimulates IGF-I production<br>• IGF-I and GH promote growth in all body tissues |
| | *Pharmacologic* | *Pharmacologic* | |
| | • α-Adrenergic agonists (eg, clonidine)<br>• β-Adrenergic antagonists (eg, propranolol)<br>• Dopamine agonists (eg, bromocriptine) in healthy individuals<br>• GABA agonists (eg, muscimol) | • Dopamine antagonists (eg, phenothiazines)<br>• α-Adrenergic antagonists (eg, phentolamine)<br>• β-Adrenergic agonists (eg, isoproterenol)<br>• Serotonin antagonists (eg, methysergide) | |
| Prolactin | *Physiologic* | *Physiologic* | |
| | • TRH<br>• VIP<br>• Estrogen<br>• Serotonin<br>• Histamine<br>• Endogenous opioids<br>• Pregnancy and nursing | • Dopamine<br>• GABA | Lactation |

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| | | | |
|---|---|---|---|
| | *Pharmacologic* | *Pharmacologic* | |
| | • Dopamine antagonists (eg, phenothiazines, haloperidol, methyldopa)<br>• Opiates<br>• Estrogens<br>• $H_2$-antagonists (eg, cimetidine)<br>• MAO inhibitors | Dopamine agonists (eg, L-dopa, bromocriptine, pergolide, cabergoline) | |
| Adrenocorticotropic Hormone (ACTH) | • CRH<br>• AVP | • Elevated cortisol<br>• Dopamine agonists<br>• Somatostatin analog (eg, pasireotide) | • Glucocorticoid effects<br>• Pigmentation |
| Thyroid-Stimulating Hormone (TSH) | • TRH<br>• Estrogens<br>• Norepinephrine<br>• Serotonin | • Thyroxine<br>• Triiodothyronine<br>• Somatostatin<br>• Glucocorticoids<br>• Dopamine | Iodine uptake and thyroid hormone synthesis |
| Luteinizing Hormone (LH) | *Physiologic* | *Physiologic* | |
| | GnRH (pulsatile) | Fasting | Ovulation |
| | *Pharmacologic* | *Pharmacologic* | Maintains corpus luteum Stimulates testosterone production |
| | Clomiphene | • Estrogen Testosterone<br>• GnRH (tonic, leuprolide) | |
| | *Physiologic* | *Physiologic* | |
| Follicle-Stimulating Hormone (FSH) | • GnRH (pulsatile)<br>• Menopause<br>• Ovarian disorders | • Estradiol<br>• Inhibin<br>• Fasting | • Ovarian follicle development<br>• Stimulates estradiol and progesterone<br>• Spermatogenesis |
| | *Pharmacologic* | *Pharmacologic* | |
| | Clomiphene | GnRH (tonic, leuprolide) | |

ADH, antidiuretic hormone; AVP, arginine-vasopressin, CRH, corticotropin-releasing hormone; GABA, *γ*-aminobutyric acid; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor-1; MAO, monoamine oxidase; TRH, thyrotropin-releasing hormone; VIP, vasoactive intestinal peptide.

*Data from References* [2–4].

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Unlike the posterior pituitary, the release of anterior pituitary hormones is not regulated by direct nerve stimulation but rather is controlled by specific hypothalamic-releasing and inhibitory hormones. The median eminence of the hypothalamus contains a large number of capillaries that converge to form a network of veins known as the *hypothalamic-hypophyseal portal circulation*. Inhibiting and releasing hormones synthesized in the neurons of the hypothalamus reach the anterior pituitary via the hypothalamic-hypophyseal portal vessels to control the release of anterior pituitary hormones. Although there is a direct arterial blood supply to the anterior pituitary lobe, the hypothalamic-hypophyseal portal vessels provide the primary blood supply (see Fig. e98-1). In contrast to the posterior pituitary, the anterior pituitary lobe is highly vascular and has the highest rate of organ blood flow in the body.

The specialized secretory cells of the anterior pituitary lobe secrete six major polypeptide hormones (see Table e98-1). These include growth hormone (GH) or somatotropin, adrenocorticotropic hormone (ACTH) or corticotropin, thyroid-stimulating hormone (TSH) or thyrotropin, prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The release of these hormones is regulated primarily by hypothalamic-releasing and inhibiting hormones. Thyrotropin-releasing hormone (TRH) stimulates the anterior pituitary to release TSH and prolactin; corticotropin-releasing hormone (CRH) stimulates the anterior pituitary to release ACTH; growth hormone-releasing hormone (GHRH) stimulates the anterior pituitary to release GH; and gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary to release LH and FSH. Hypothalamic release of somatostatin inhibits the release of GH, and hypothalamic release of dopamine (aka prolactin inhibitory hormone) inhibits prolactin secretion. Prolactin differs from the other anterior lobe hormones in that an inhibiting factor, rather than a stimulating factor, is primarily responsible for controlling its secretion. In the absence of hypothalamic input, prolactin is produced in excess, whereas other anterior pituitary hormones become deficient. The physiologic regulation and action of posterior and anterior pituitary hormones are summarized in Table e98-1.[2–4]

Destruction of the pituitary gland may result in secondary hypothyroidism, hypogonadism, adrenal insufficiency, GH deficiency, and hypoprolactinemia. The formation of certain types of pituitary tumors may result in pituitary hormone excess. Pituitary tumors may physically compress the pituitary and prevent the release of hypothalamic factors that regulate pituitary hormones.

In this chapter, the pathophysiology and the role of pharmacotherapy in the treatment of acromegaly, short stature, hyperprolactinemia, and panhypopituitarism are discussed.

## GROWTH HORMONE

GH has direct anti-insulin effects on lipid and carbohydrate metabolism. GH decreases the utilization of glucose by peripheral tissues, increases lipolysis, and increases muscle mass. GH also stimulates gluconeogenesis in hepatocytes, impairs tissue glucose uptake, diminishes insulin-receptor sensitivity, and impairs post-receptor insulin action. The growth-promoting effects of GH are primarily mediated by insulin-like growth factors (IGFs), also known as *somatomedins*. GH stimulates the formation of IGF-1 in the liver as well as in other peripheral tissues. This anabolic peptide acts as a direct stimulator of cell proliferation and growth. There are two types of IGFs: IGF-1 and IGF-2. IGF-1 regulates growth to some extent before, and largely after, birth. In contrast, IGF-2 is thought to primarily regulate growth in utero.[5] GH is secreted by the anterior pituitary in a pulsatile fashion, with several short bursts that occur mostly at night. Because of the short half-life of GH in the plasma (~30 minutes), measurements of circulating GH concentrations throughout the waking hours usually are very low or undetectable. Daytime GH pulses are most likely to occur after meals, following exercise, or during periods of stress. The greatest amount of GH secretion occurs during the night within the first 1 to 2 hours of slow-wave sleep (stage III or IV). Secretion of GH is lowest during infancy, increases slightly during childhood, reaches its peak during adolescence, and then begins to gradually decline during the middle-age years.[3]

## ACROMEGALY

Acromegaly is a pathologic condition characterized by excessive production of GH. This is a rare disorder with prevalence ranging between 2.8 and 13.7 cases per 100,000 and incidence rates ranging between 0.2 and 1.1 cases per 100,000 people.[6] Gigantism, which is rarer than acromegaly, is the excess secretion of GH prior to epiphyseal closure in children.[7] Patients diagnosed with acromegaly have a two- to threefold increase in mortality, usually related to cardiovascular, respiratory, or neoplastic disease.[7-10] Most patients are middle-aged at the time of diagnosis, and this disorder does not appear to affect one sex to a greater extent than the other.[6] The most common cause of excess GH secretion in acromegaly is a GH-secreting pituitary adenoma, accounting for over 95% of all cases.[7] Rarely, acromegaly is caused by ectopic GH-secreting adenomas, GH cell hyperplasia, excess GHRH

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secretion, or is a manifestation of multiple endocrine neoplasia syndrome type 1, McCune–Albright syndrome, or the Carney complex, all very rare hypersecretory endocrinopathies.[7–9]

The clinical signs and symptoms of acromegaly develop gradually over an extended period of time. The changes in physical appearance caused by GH excess are slow and subtle to develop. Thus, most patients are not diagnosed with acromegaly until 7 to 10 years after the presumed onset of excessive GH secretion.[9] Excessive secretion of GH and IGF-1 adversely affects several organ systems. Almost all patients with acromegaly will present with physical signs and symptoms of soft-tissue overgrowth. Table e98-2 summarizes the classic clinical presentation of patients with acromegaly.[7–9] Some patients with acromegaly present with only a few of these classic signs and symptoms, making recognition of this disease extremely difficult.

TABLE e98-2

**Clinical Presentation of Acromegaly**

**General**

The patient will experience slow development of soft-tissue overgrowth affecting many body systems. Signs and symptoms may gradually progress over many years.

**Symptoms**

The patient may complain of symptoms related to local effects of the GH-secreting tumor, such as headache and visual disturbances. Other symptoms related to elevated GH and IGF-1 concentrations include excessive sweating, neuropathies, joint pain, and paresthesias.

**Signs**

The patient may exhibit coarsening of facial features, increased hand volume, increased ring size, increased shoe size, an enlarged tongue, and various dermatologic conditions.

**Laboratory tests**

The patient's GH concentration will be more than 1 mcg/L (45 pmol/L) following an OGTT, and IGF-1 serum concentrations will be elevated. Glucose intolerance may be present in up to 50% of patients.

**Common Comorbid Conditions**

- Cardiovascular diseases such as hypertension, coronary heart disease, cardiomyopathy, and left ventricular hypertrophy are common in patients with acromegaly.
- Osteoarthritis and joint damage develop in up to 90% of acromegalic patients.
- Respiratory disorders and sleep apnea occur in up to 60% of acromegalic patients.
- Type 2 diabetes develops in approximately 25% of acromegalic patients.
- Patients with acromegaly may be at higher risk of developing esophageal, colon, and stomach cancer.

OGTT, oral glucose tolerance test.

*Data from References* [7–9].

The diagnosis of acromegaly is based on a combination of diagnostic tests and clinical signs and symptoms. Random measures of plasma GH levels are not dependable because of the pulsatile pattern of release. However, some clinicians exclude the diagnosis of acromegaly in the presence of a random GH below 0.4 mcg/L (18 pmol/L) and IGF-1 that is normal for age and sex.[7–9] The oral glucose tolerance test (OGTT) is commonly used as an important diagnostic tool. Postprandial hyperglycemia inhibits the secretion of GH for at least 1 to 2 hours. Therefore, an oral glucose load would be expected to suppress GH concentrations. However, patients with acromegaly continue to secrete GH during the OGTT. Because GH stimulates the production of IGF-1, serum IGF-1 concentration is often measured as the initial screening test in the diagnosis of acromegaly. Circulating IGF-1 is cleared from the body at a much slower rate than is GH, and measurements can be collected at any time of the day to identify patients with GH excess.[7–9] Current criteria for the diagnosis of acromegaly include failure of GH suppression to less than 1 mcg/L (45 pmol/L) following an OGTT in the presence of elevated IGF-1 serum concentrations (strong recommendation, moderate quality of evidence).[7,8,11] With the development of more sensitive GH and IGF-1 assays, the American Association of Clinical Endocrinologists (AACE) suggests lowering the cutoff for GH suppression to less than 0.4 mcg/L (18 pmol/L), although other groups still support a cutoff of less than 1 mcg/L based on concerns of requisite sensitivity of many assays.[7,8,11] Insulin-like growth factor 1

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binding protein 3 (IGFBP-3) is positively regulated by GH and binds to circulating IGF-1 with high affinity. In the future, this test may prove useful for monitoring the response to therapy but AACE does not currently recommend IGFBP-3 measurements to guide treatment decisions.[8] Computed tomography and magnetic resonance imaging (MRI) of the pituitary are important diagnostic tests to confirm the presence of a pituitary adenoma.[7,8,11]

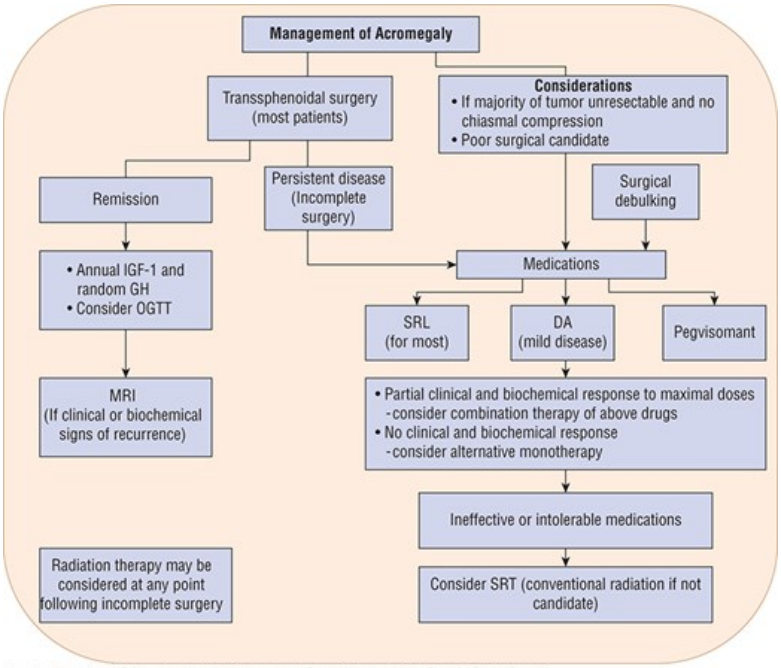
## Treatment

The primary treatment goals for patients diagnosed with acromegaly are to reduce GH and IGF-1 concentrations, improve the clinical signs and symptoms of the disease, and decrease mortality.[7,8,11-14] Many clinicians define biochemical control of acromegaly as suppression of GH concentrations to less than 1 mcg/L (45 pmol/L) after a standard OGTT in the presence of normal IGF-1 serum concentrations. However, some experts have proposed a lower cutoff GH value of 0.4 mcg/L (18 pmol/L) due to the availability of more sensitive test methods.[12] The treatment of choice for most patients with acromegaly is transsphenoidal surgical resection of the GH-secreting adenoma (strong recommendation, moderate quality evidence).[7,8,11-13] Postsurgical cure rates have been reported to range from 50% to 90%, depending on the type of adenoma and the expertise of the neurosurgeon.[7,8,13] Complications of transsphenoidal surgery are relatively infrequent and include cerebrospinal fluid leak, meningitis, arachnoiditis, diabetes insipidus, and pituitary failure.[8] For patients who are poor surgical candidates, those who have not responded to surgical or medical interventions, or others who refuse surgical or medical treatment, radiation therapy may be considered. However, radiation therapy may require several years before the symptoms of acromegaly are relieved.

Because neither radiation therapy nor surgery will cure all patients with acromegaly, adjuvant drug therapy is often needed to control symptoms.[7,8,11,12] Figure e98-2 shows a treatment algorithm for the management of acromegaly.[7,8]

**FIGURE e98-2**

Treatment algorithm for acromegaly. (DA, dopamine agonist; SRL, somatostatin analog; SRT, stereotactic radiotherapy) (*Reprinted, with permission, from Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:3933–3951. Copyright 2014, The Endocrine Society.*)



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### Pharmacologic Therapy

1 Drug therapy should be considered primary therapy for patients with acromegaly who prefer medical therapy, are poor surgical candidates, or


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when there is a poor likelihood of surgical success. In addition, drug therapy should be considered as adjunctive therapy in the presence of persistent disease after surgery (strong recommendation, high-quality evidence).[7,8] The most common pharmacologic treatment options include dopamine agonists, somatostatin analogs, and the GH-receptor antagonist pegvisomant. Dopamine agonists such as bromocriptine and cabergoline are effective in a small subset of patients. Their principal advantages are oral administration and lower cost. Somatostatin analogs are more effective than dopamine agonists, reducing GH concentrations and normalizing IGF-1 in approximately 50% to 60% of patients. Pegvisomant, a GH-receptor antagonist, is highly effective in normalizing IGF-1 concentrations in up to 97% of patients in the first year and in 60% over 5 years.

### Dopamine Agonists

In normal healthy adults, dopamine agonists cause an increase in GH production. However, when these agents are given to patients with acromegaly, there is a paradoxical decrease in GH production. The greatest clinical experience with the use of dopamine agonists in acromegaly has been with bromocriptine or cabergoline. Other agents such as pergolide, quinagolide, and lisuride also have been used but are not available in the United States. Bromocriptine and cabergoline are semisynthetic ergot alkaloids that act as dopamine-receptor agonists. Most trials assessing the efficacy of bromocriptine in the treatment of acromegaly were conducted in the 1970s and early 1980s and determined that bromocriptine was effective in suppressing serum GH levels to less than 5 mcg/L (225 pmol/L) in approximately 20% of patients.[15] While only 10% of patients experience a normalization of IGF-1 concentrations with bromocriptine therapy, more than 50% of patients treated with bromocriptine experience improvement in symptoms of acromegaly.[8,15] Cabergoline is used more commonly than bromocriptine.[8] A meta-analysis of 15 studies concluded that cabergoline as monotherapy was effective in normalizing IGF-1 levels in 34% of patients and resulted in normalization of IGF-1 levels in 52% of patients when added to a somatostatin analog in those unresponsive to somatostatin analog monotherapy.[16]

In the United States, bromocriptine is commercially available as 0.8- and 2.5-mg oral tablets and 5-mg oral capsules. The 0.8-mg tablet is only approved for adjunctive therapy in type 2 diabetes mellitus. In acromegalic patients, significant reductions in GH concentrations are observed within 1 to 2 hours of oral dosing. This effect persists for at least 4 to 5 hours. An overall clinical response in acromegalic patients typically occurs after 4 to 8 weeks of continuous bromocriptine therapy. For treatment of acromegaly, bromocriptine is initiated at a dose of 1.25 mg (1/2 of a 2.5-mg tablet) at bedtime and is increased by 1.25-mg increments every 3 to 4 days as needed. Doses as high as 86 mg/day have been used for the treatment of acromegaly, but clinical studies have shown that dosages more than 20 to 30 mg daily do not offer additional benefits in the suppression of GH. When used for the treatment of acromegaly, the duration of action of bromocriptine is shorter than that for the treatment of hyperprolactinemia. Therefore, the total daily dose of bromocriptine should be divided into three or four doses.

Cabergoline is commercially available as 0.5-mg tablets. Use in acromegaly is considered off-label. Dosing is typically initiated at 0.5 mg twice weekly and increased as needed to 0.5 mg every other day. Doses up to 7 mg/wk (0.5 mg twice daily) have been used in clinical trials.

The most common adverse effects of dopamine agonist therapy include CNS symptoms such as headache, lightheadedness, dizziness, nervousness, and fatigue. GI effects such as nausea, abdominal pain, or diarrhea also are very common. Some patients may need to take dopamine agonists with food to decrease the incidence of adverse GI effects. Most adverse effects are seen early in the course of therapy and tend to decrease with continued treatment.[8,15] Dopamine agonists may cause the thickening of bronchial secretions and nasal congestion. Rare cases of psychiatric disturbances, pleural diseases, and an erythromelalgic syndrome (painful paroxysmal dilation of the blood vessels in the skin of the feet and lower extremities) have been reported with dopamine agonist use. These conditions appear to be associated with higher doses and prolonged duration of therapy.[8,15]

Dopamine agonists are not FDA-approved for use during pregnancy. However, surveillance of women who took dopamine agonists throughout pregnancy does not suggest that dopamine agonists are associated with an increased risk for birth defects.[17] If a woman becomes pregnant while taking dopamine agonists, the risks and benefits of therapy should be discussed with the patient. In most cases, the benefits of successful therapy outweigh the risks, and dopamine agonist therapy should be continued if symptoms have improved and GH concentrations have been reduced.

Given the potential cost advantages and convenience of oral administration, dopamine agonists are often considered for treatment of acromegaly prior to initiation of somatostatin analogs. The Endocrine Society guidelines suggest a trial of a dopamine agonist in acromegalic patients with mild signs and symptoms and modest elevations in serum IGF-1 (weak recommendation, low-quality evidence).[7] However, long-acting somatostatin analogs are considered a more attractive first-line treatment option for acromegaly.

### Somatostatin Analogs

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Octreotide, lanreotide, and pasireotide are long-acting somatostatin analogs that are more potent in inhibiting GH secretion than endogenous somatostatin.[18] The Endocrine Society suggests somatostatin analogs as initial adjuvant medical therapy in patients with significant disease (weak recommendation, low-quality evidence) and as primary therapy in patients who cannot be cured by surgery or are poor surgical candidates (weak recommendation, moderate-quality evidence).[7] These agents also suppress the LH response to GnRH; decrease splanchnic blood flow; and inhibit secretion of insulin, vasoactive intestinal peptide (VIP), gastrin, secretin, motilin, serotonin, and pancreatic polypeptide. Pasireotide is a somatostatin analog that has a broader affinity for somatostatin receptor subtypes than octreotide or lanreotide, and this may result in greater GH inhibition. Pasireotide is also effective for octreotide or lanreotide-resistant adenomas.[18]

Octreotide (Sandostatin) injection is commercially available in the United States for subcutaneous or IV administration. A long-acting intramuscular formulation of octreotide (Sandostatin LAR) is available for monthly administration. An oral formulation of octreotide (Mycapssa) is also available for those who respond to and tolerate injectable octreotide or lanreotide.[19] In addition to the treatment of acromegaly, octreotide has many other therapeutic uses, including the treatment of carcinoid tumors, vasoactive intestinal peptide-secreting tumors (VIPomas), GI fistulas, variceal bleeding, diarrheal states, and irritable bowel syndrome.

The efficacy of octreotide for the treatment of acromegaly was initially determined by two major multicenter trials.[20,21] These studies demonstrated that drug therapy with octreotide suppresses mean serum GH concentrations to less than 5 mcg/L (225 pmol/L) and normalizes serum IGF-1 concentrations in 50% to 60% of patients, and reduces the clinical signs and symptoms of acromegaly. In a 6-month multicenter trial, 70% of patients experienced significant relief of headaches.[21] In some patients, relief of headache symptoms occurred within minutes of octreotide administration. In addition, middle-finger circumference was reduced significantly, and 50% to 75% of patients experienced an improvement in symptoms of excessive perspiration, fatigue, joint pain, and cystic acne. Long-term follow-up of patients with acromegaly treated with octreotide LAR for up to 9 years showed therapy to be safe and effective.[22] Octreotide also has been shown to improve the cardiovascular manifestations of acromegaly and to halt pituitary tumor growth, with some patients experiencing tumor regression.[23] Shrinkage of pituitary tumor mass occurs in approximately 50% of patients.[24]

The pharmacodynamic effects of long-acting octreotide are similar to those of subcutaneously administered octreotide. Single monthly doses of long-acting octreotide have been shown to be at least as effective as daily doses of subcutaneous octreotide administered in divided doses three times daily in normalizing IGF-1 levels and maintaining suppression of mean serum GH concentrations.[25] Trials evaluating the efficacy of long-acting octreotide in patients who previously responded to subcutaneously administered octreotide have reported sustained suppression of GH concentrations to less than 5 mcg/L (225 pmol/L) and normalization of IGF-1 in patients following 1 year of therapy.[25] Trials evaluating oral octreotide in patients who responded to injectable octreotide or lanreotide found that 60% of patients maintained a response for 9 months based on IGF-1 levels.[19]

Response to therapy with octreotide is related to the presence and increased quantity of functioning somatostatin receptors located in the pituitary adenoma. Identification of patients who will most likely respond to octreotide prior to initiation of long-term therapy is important given the high cost of this medication and the inconvenience of subcutaneous or intramuscular drug administration. Suppression of serum GH concentrations after a single 50-mcg dose of octreotide has been used to predict a favorable long-term response to octreotide therapy, but the reliability of this test is not universally accepted.[7,26]

The initial dose of injectable octreotide for treatment of acromegaly is typically 100 mcg administered three times daily followed by either titration to a maximum of 1,500 mcg/day or transition to long-acting octreotide.[8] Some clinicians recommend a starting dose of 50 mcg every 8 hours, then increasing the dose to 100 mcg every 8 hours after 1 week, to improve the patient's tolerance of adverse GI effects. The dose can be increased by increments of 50 mcg every 1 to 2 weeks based on mean serum GH and IGF-1 concentrations. Patients who experience a significant rise in GH prior to the end of the 8-hour dosing interval may benefit from decreasing the dosing interval to every 4 to 6 hours. Although doses as high as 1,500 mcg/day have been used, doses greater than 600 mcg daily generally do not offer additional benefits, and most patients are adequately managed with 100 to 200 mcg three times daily.[8] Patients who have been maintained on subcutaneous octreotide for at least 2 weeks and have shown response to therapy can be converted to the long-acting depot form of octreotide. The initial dose of long-acting octreotide is 20 mg administered intramuscularly in the gluteal region every 28 days. Steady-state serum concentrations are not obtained until after 3 months of therapy. Therefore, dosage adjustments for long-acting octreotide should not be considered until after the 3rd dose. Some patients may require additional subcutaneous injections during the initial dose-titration phase in order to control symptoms. In patients who achieve more than 50% reduction in GH levels, the dose should be increased to 30 mg every 4 weeks. Some patients may require as much as 60 mg every 4 weeks.[27] In patients who have responded to and tolerated injectable

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octreotide or lanreotide, oral octreotide can be initiated on the day of a scheduled injection at a dose of 20 mg twice daily. The dose can be increased by 20 mg per day every 2 to 4 weeks based on IGF-1 levels and the patient's signs and symptoms to a maximum of 40 mg twice daily. As the oral formulation of octreotide exhibits pH-dependent absorption, clinicians should avoid drugs that increase gastric pH (eg, proton pump inhibitors) to maximize bioavailability.

Lanreotide (Somatuline Depot) is commercially available in the United States for monthly, deep subcutaneous administration. In addition to acromegaly, lanreotide is also indicated for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and carcinoid syndrome. The efficacy of lanreotide for the treatment of acromegaly has been evaluated in several prospective multicenter clinical trials involving treatment-naïve and treatment-experienced patients who were switched from intramuscular octreotide LAR or intramuscular lanreotide LA to monthly deep subcutaneous lanreotide.[28] These studies have determined that deep subcutaneous lanreotide suppresses mean serum GH concentrations to less than 5 mcg/L (225 pmol/L) and normalizes serum IGF-1 concentrations to a similar extent as octreotide LAR and lanreotide LA. A 4-year follow-up of 23 patients treated with monthly deep subcutaneous lanreotide reported the drug to be well tolerated during long-term therapy with mean serum GH concentrations less than 5 mcg/L (225 pmol/L) in 62% of patients and normalization of serum IGF-1 concentrations in 43% of patients.[29] Analyses of trials investigating the effects of lanreotide on pituitary tumor mass have shown shrinkage in the majority of patients, and the response appears to be more prevalent in treatment-naïve patients and in patients with macroadenomas.[28,30] Well-designed trials directly comparing the efficacy of intramuscular octreotide LAR to deep subcutaneous lanreotide are currently lacking. However, these two agents are generally regarded to have comparable efficacy.[7,8]

Lanreotide (Somatuline Depot) is commercially available in the United States as 60-, 90-, and 120-mg prefilled syringes. In contrast to octreotide LAR and pasireotide, lanreotide does not need to be reconstituted prior to administration. The initial recommended dose of lanreotide is 90 mg given by deep subcutaneous injection in the superior external quadrant of the buttock every 28 days. Injection sites should be alternated between the left and right sides. The initial dose should be reduced to 60 mg every 28 days for patients with moderate or severe renal or hepatic impairment. After 3 months of therapy, the dose may then be titrated and/or frequency extended, based on serum GH concentrations, serum IGF-1 concentrations, and control of signs and symptoms of acromegaly.[28] Patients well controlled on lanreotide 60 or 90 mg every 28 days may consider an extended dosing interval of lanreotide 120 mg every 6 to 8 weeks. Increases in drug frequency greater than every 28 days or higher than 120 mg may be recommended for patients with partial responses to lanreotide.[31]

Pasireotide (Signifor LAR) for the treatment of acromegaly is commercially available in the United States in the form of a monthly intramuscular injection. Another formulation of pasireotide (Signifor) is approved for treatment of Cushing disease as a twice-daily subcutaneous injection. The efficacy of the long-acting pasireotide formulation has been evaluated in both drug-naïve patients and those inadequately controlled on long-acting octreotide or lanreotide.[32–35] In drug-naïve patients treated for 12 months, pasireotide suppressed mean serum GH concentrations to less than 2.5 mcg/L (113 pmol/L) and normalized serum IGF-1 concentrations in 38% compared to 23% with octreotide.[33] An extension study of up to 25 months noted long-term biochemical control (GH < 2.5 mcg/L [113 pmol/l] and normal IGF-1) in 48% with pasireotide compared with 45% with octreotide.[34] In patients inadequately controlled with octreotide or lanreotide, pasireotide resulted in biochemical control (GH <2.5 mcg/L [113 pmool/L]and normal IGF-1) in 15% to 20% of patients treated for 24 weeks.[35]

The initial recommended dose of pasireotide is 40 mg given by intramuscular injection every 28 days. The initial dose should be reduced to 20 mg every 28 days for patients with moderate or severe hepatic impairment. After 3 months of therapy, the dose may be titrated based on serum GH concentrations, serum IGF-1 concentrations, and control of signs and symptoms of acromegaly. Doses of pasireotide exceeding 60 mg every 28 days are not recommended.[32]

The most common adverse effects of somatostatin analog therapy are GI disturbances such as diarrhea, nausea, abdominal cramps, malabsorption of fat, and flatulence.[25,28,32] GI adverse effects occur in approximately 75% of patients but usually subside within 10 to 14 days of continued treatment. Octreotide can cause injection-site pain (4%-31%), conduction abnormalities and arrhythmias (9%), subclinical hypothyroidism (2%-12%), biliary tract disorders (4%-50%), and abnormalities in glucose metabolism (2%-18%). Lanreotide has been associated with injection-site reactions (9%), sinus bradycardia (3%), hypertension (5%), biliary tract disorders (20%), and abnormalities in glucose metabolism (7%). While adverse effects with pasireotide are similar to octreotide and lanreotide, the incidence of hyperglycemia is significantly greater (61%-67% vs 25%-30%), often requiring treatment with antidiabetes medications (38%-39% vs 6%).

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Somatostatin analogs also inhibit cholecystokinin release and gallbladder motility, predisposing patients to the development of cholelithiasis.[36,37] The development of gallstones is a long-term adverse effect of somatostatin analog therapy and is dependent mainly on geographic factors, dietary habits, and length of treatment. The incidence of gallstones in patients with acromegaly receiving octreotide and lanreotide increases with the duration of therapy and has been reported to range from 20% to 50%.[25,28,32] However, most patients are asymptomatic, and the diagnosis of cholelithiasis usually is made following an ultrasonographic study that is not prompted by patient symptoms. It has been estimated that only 1% of patients will develop symptomatic gallstones during 1 year of octreotide treatment.[36] Because somatostatin analog-induced gallstones usually are present without symptoms, prophylactic cholecystectomy or medical therapy with ursodeoxycholic acid is not recommended. A small number of studies have suggested that the incidence of gallstone development may be lower with long-acting octreotide compared to subcutaneous octreotide.[25] However, further studies are needed to confirm this observation.

3 The effect of somatostatin analogs on glucose metabolism in patients with acromegaly is multifactorial. Decreases in serum GH concentrations induced by somatostatin analogs should result in decreased hepatic gluconeogenesis and increased insulin-receptor sensitivity. However, somatostatin analogs also decrease insulin secretion and increase IGFBP-1, which is known to inhibit the insulin-like effects of IGF-1. In addition, somatostatin analogs delay the GI absorption of glucose, which may further alter glucose metabolism in patients with acromegaly.[38] Patients with diabetes should be actively monitored and glucose-lowering medications adjusted accordingly.[39] Risk factors associated with worsening glucose tolerance included female sex and elevated baseline insulin concentrations. Although somatostatin analogs have a beneficial effect on glucose tolerance in most patients, glucose determinations should be obtained frequently in the early stages of therapy.

#### Growth Hormone Receptor Antagonist

4 Pegvisomant (Somavert) is a genetically engineered GH derivative that binds to, but does not activate, GH receptors and inhibits IGF-1 production. This agent is different from other medications used in the management of acromegaly because it does not inhibit GH production; rather, it blocks the physiologic effects of GH on target tissues. Therefore, GH concentrations remain elevated during therapy, and response to treatment is evidenced by a reduction in IGF-1 concentrations. Unlike somatostatin analogs, the pharmacologic activity of pegvisomant does not depend on the presence and quantity of somatostatin receptors in the pituitary tumor.[40] Studies evaluating the efficacy of pegvisomant have reported a dose-dependent normalization of IGF-1 concentrations in 54% to 89% of patients after 12 weeks of therapy and in 97% of patients after 1 year of therapy.[40,41] Significant improvements in the clinical signs and symptoms of acromegaly were reported and persisted throughout the 1-year treatment period.[41] An ongoing, international postmarketing surveillance registry (ACROSTUDY) reported normalization of IGF-1 serum concentrations in 73% of patients treated with pegvisomant for 10 years. Investigators note that failure to maintain IGF-1 normalization may reflect suboptimal dosing or more advanced disease than reported in the original studies.[42]

Adverse effects include injection-site pain, GI complaints such as nausea and diarrhea, and flu-like symptoms. Significant elevations in hepatic aminotransferase concentrations, which are generally reversible after discontinuation of the drug, have been reported.[43] Hepatic function tests should be monitored very closely during therapy as outlined in the product labeling and the drug should be used with caution in patients with baseline elevations in hepatic aminotransferase concentrations. GH concentrations may increase significantly during the first 6 months of pegvisomant therapy. Tumor growth has been reported in a small number of patients and there are theoretical concerns that the lack of GH feedback regulation on tumors that lead to persistently elevated GH concentrations may stimulate tumor growth or result in other long-term adverse effects. Results of the ongoing ACROSTUDY suggest that the rate of tumor growth is comparable to the background rate in acromegaly, and the incidence of hepatic aminotransferases greater than three times the upper limit of normal is low (3%).[42]

Pegvisomant is commercially available in the United States for daily subcutaneous use. It is recommended by the manufacturer that the initial 40-mg loading dose be administered under direct supervision by a physician but some authors note this is rarely done. Subsequent doses are self-administered by the patient starting at a dose of 10 mg daily. The dose can be adjusted in 5-mg increments based on serum IGF-1 concentrations every 4 to 6 weeks. The typical maintenance dose is 10 to 30 mg daily. Higher doses (40-60 mg daily) have been reported in patients who are younger, overweight, or have diabetes or high baseline IGF-1 levels.[43]

Based on high response rates in clinical trials, pegvisomant appears to be among the most effective agent for normalizing IGF-1 serum concentrations. Current guidelines for acromegaly management suggest pegvisomant therapy for patients who have failed to achieve normalization of IGF-1 serum

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concentrations with other treatments or as the initial adjuvant medical therapy (weak recommendation, low-quality evidence).[7,8,11]

#### Combination Therapy

Several small studies have suggested that combination therapy with somatostatin analogs, dopamine agonists, or pegvisomant may be more effective than monotherapy.[7,8] Several of these trials have used doses lower than those typically used for monotherapy in order to reduce the risk of adverse effects. The Endocrine Society recommends the addition of pegvisomant or cabergoline in patients with inadequate response to a somatostatin analog (weak recommendation, low-quality evidence).[7] Because of the potential for additive adverse effects, combination therapy should be considered as a therapeutic option only for refractory patients who have not fully responded to monotherapy.[7,8,46]

### Evaluation of Therapeutic Outcomes

Appropriate monitoring of medical therapy for acromegaly incorporates assessing for control of biochemical targets and clinical symptoms. An age-normalized serum IGF-1 and random GH are used to guide dosing and frequency of administration, and it is recommended to periodically assess these parameters as they correlate with disease control. Clinical symptoms that may relate to the tumor size (eg, headaches, visual disturbances) or elevations in GH or IGF-1 (eg, excessive sweating, arthralgia) should also be assessed periodically. Additional laboratory tests to monitor adverse events include serum glucose, for somatostatin analogs, and hepatic aminotransferases, for pegvisomant.

### Conclusion

Acromegaly is a chronic debilitating disease characterized by excess GH secretion, most commonly caused by a GH-secreting pituitary adenoma. Transsphenoidal surgical resection of the adenoma is the current treatment of choice for most patients with acromegaly. Patients who are poor surgical candidates may receive radiation therapy or long-term pharmacologic therapy. Drug therapy options within the United States for acromegaly include dopamine agonists, somatostatin analogs, and pegvisomant.

## GROWTH HORMONE DEFICIENCY

Short stature is a condition that is commonly defined by a physical height that is more than two standard deviations below the population mean for a given age, sex, and population.[47] It has been estimated that 2% of the population can be characterized as having short stature, although growth hormone deficiency as the primary cause is rare (estimated prevalence 1 in 4,000).[47] Short stature is a very broad term with many etiologies. A true lack of GH is among the least common causes and is known as GHD short stature. The etiology of GH deficiency may be congenital, resulting from various genetic abnormalities, such as GHRH deficiency, GH gene deletion, and developmental disorders including pituitary aplasia or hypoplasia; or acquired, resulting from hypothalamic or pituitary tumors, neurosurgery, cranial irradiation, head trauma, pituitary infarction, and CNS infections. However, the etiology is unclear in many cases, with no evidence of cranial pathology or known genetic abnormalities. In addition, psychosocial deprivation, hypothyroidism, poorly controlled diabetes mellitus, treatment of precocious puberty with LH-releasing hormone agonists, and pharmacologic agents such as glucocorticoids, methylphenidate, and dextroamphetamine may induce transient GH insufficiency.

Short stature also occurs with several conditions that are not associated with GH deficiency or insufficiency. These conditions include intrauterine growth restriction; constitutional growth delay; malnutrition; malabsorption of nutrients associated with inflammatory bowel disease, celiac disease, and cystic fibrosis; chronic renal failure; skeletal and cartilage dysplasia; and genetic syndromes such as Turner syndrome.[47,48] In addition, many children are diagnosed with idiopathic or normal variant short stature. These patients have heights that are significantly lower than the third percentile but have normal GH serum concentrations and no specific underlying explanation for short stature.[48]

Children with congenital GHD usually are born with an average birth weight. Decreases in growth velocity generally become evident between the ages of 6 months and 3 years.[47] In contrast, GH insufficiency may arise at any age during growth and development. The clinical characteristics of GHD or GH-insufficient children are listed in Table e98-3.[47]

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TABLE e98-3

**Clinical Presentation of Short Stature**

**General**

- The patient will have a physical height that is greater than two standard deviations below the population mean for age and sex.

**Signs**

- The patient will present with reduced growth velocity and delayed skeletal maturation.
- Children with GH-deficient or GH-insufficient short stature may also present with central obesity, prominence of the forehead, and immaturity of the face.

**Laboratory tests**

- The patient will exhibit a peak GH concentration <10 mcg/L (450 pmol/L) following a GH provocation test. Reduced IGF-1 and concentrations may be present.
- Because GH deficiency may be accompanied by loss of other pituitary hormones, hypoglycemia and hypothyroidism may be noted.

GH, growth hormone.

*Data from References* [48,49].

Several factors must be considered in the diagnosis of GH deficiency or insufficiency. Standard epidemiologic growth charts developed by the National Center for Health Statistics typically are used to determine the percentile of anthropometric measurements, such as height, weight, and head circumference. Pubertal stage typically is determined using the Tanner method. Bone age is determined according to published standards, and growth velocity is calculated to determine the patient's height velocity percentile using standard growth-velocity charts.[47,48] GH deficiency is rarely seen in the absence of delayed skeletal maturation and decreased growth velocity. In addition, several provocative stimuli that induce GH secretion may be used diagnostically to determine GH status. Provocative pharmacologic GH stimuli include insulin-induced hypoglycemia, clonidine, L-dopa, arginine, glucagon, macimorelin and GHRH.[47] Traditionally, a subnormal GH response during childhood is arbitrarily defined as a peak GH serum concentration less than 10 mcg/L (450 pmol/L) during a 2-hour period after administration of one of these agents.[47] However, a lower cutoff may be used for the peak GH response, depending on the specific assay and GH reference product used. For prepubertal boys (>11) and girls (>10), priming with sex hormones to improve the specificity of GH provocation tests is suggested by the Pediatric Endocrine Society (conditional, low quality). Some patients exhibit clinical signs of GH deficiency, subnormal growth velocity, and delayed bone age despite GH levels that are within normal limits after provocative testing. This makes diagnosis in this group of patients very difficult. Diagnosis based on GH stimulation tests becomes further complicated because of the paucity of data reporting the normal range of GH concentrations after provocative testing in healthy children and the fact that commercial GH and IGF-1 assays currently available may not be equivalent. Although a gold standard for diagnosis of GHD does not exist, treatment is generally recommended for children who have "idiopathic short stature" and pass GH provocative testing but have most of the following criteria: height greater than 2.25 standard deviations below the mean for age, subnormal growth velocity; delayed bone age, low serum IGF-1 and/or IGFBP-3, and other clinical features consistent with GH deficiency.[47,49] Ultimately, careful consideration of multiple factors by a pediatric endocrinology specialist is required to correctly diagnose GH deficiency. Of note, more than half of children diagnosed with GH deficiency are found to secrete normal quantities of GH and IGF-1 in adulthood.[50]

## Treatment

### Pharmacologic Therapy

The treatment of GH deficiency with pituitary-derived human GH was first reported in the late 1950s.[51] Until the 1980s, GH was extracted from human pituitary tissue and the supply was very limited. Today, GH is produced using recombinant DNA technology and enables a much larger population to receive treatment.

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5 Recombinant GH is currently considered the drug of choice for GHD short stature. GH replacement therapy in children with documented GHD short stature produces a significant improvement in growth velocity within the first year of therapy and significantly improves final adult height.[52,53] The initial increase in growth velocity often is referred to as *catch-up growth*. Studies evaluating the adult height of children who received recombinant GH therapy with currently recommended dosing regimens have reported average final adult heights ranging from 0.5 to 1.7 standard deviations below the population mean. Initiation of therapy at an early chronologic age, prior to the onset of puberty, is associated with a more favorable increase in final height.[47,52–55] Therefore, prompt diagnosis of GH deficiency and early initiation of replacement therapy with recombinant GH are crucial factors in optimizing the final adult height of children with GH deficiency.

The majority of short children in the United States do not have an identifiable medical cause for their condition, but with the widespread availability of several recombinant GH formulations, many children have received GH therapy regardless of the underlying etiology of their short stature. The use of recombinant GH therapy in children with non-GHD short stature, also referred to as idiopathic short stature (ISS), has been studied by many investigators and was approved by the FDA in 2003.[48] However, the use of GH therapy in this patient population remains controversial.[56,57] The Pediatric Endocrine Society recommends against routine use of GH in every child with ISS and suggests use only after assessment of physical and psychological burdens, along with a discussion of risks and benefits.[49] A meta-analysis of 38 clinical studies evaluating the efficacy of GH treatment in children with idiopathic short stature reported average increases in a final adult height of 4 to 5 cm (1.6-2 in.) following a mean duration of therapy of 4.7 years.[58] This corresponded to an increase above the predicted adult height of 0.56 to 0.63 standard deviations of the population mean. A more recent systematic review of GH treatment in idiopathic short stature noted that the final adult height gain is usually less than that seen in other FDA-approved conditions associated with growth failure, increasing adult height by about 4 cm (1.6 in.). The individual response to therapy is highly variable, and further studies are needed to identify responders.[59]

Recombinant GH has been shown to increase the short-term growth rate in pediatric patients with chronic renal insufficiency, Turner syndrome, idiopathic short stature, Prader–Willi syndrome, short stature homeobox gene (SHOX) deficiency, Noonan syndrome, and children born small for gestational age (SGA), and is approved by the FDA for treatment of growth failure associated with these conditions. GH is also FDA-approved for the treatment of adult GH deficiency, short bowel syndrome in patients receiving specialized nutritional support, and acquired immunodeficiency syndrome wasting syndrome. Adult patients with GH deficiency during childhood must have the diagnosis of GHD confirmed when they are adults. Long-term GH therapy in GHD adults significantly decreases body fat, increases muscle mass, and improves exercise capacity.[50] GH therapy in adults has not been definitively shown to improve the cardiac risk profile or bone mineral density, but it does appear to improve psychological well-being.[60] The Beers Criteria of the American Geriatrics Society recommends avoiding GH therapy except as replacement after pituitary gland removal because the risks in older adults outweigh any potential benefits[61] (strong recommendation, high-quality evidence).[59]

6 Nine different recombinant GH products (somatropin) currently are available for use in the United States (Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Serostim, Zomactin, and Zorbtive). A once-weekly analog of GH (somapacitan, Sogroya) has also been approved for adults and is currently undergoing phase 3 clinical trials in children. A once-weekly prodrug of somatropin (lonapegsomatropin, Skytrofa) has been approved for use in children and is currently under investigation for use in adults. Somatropin is composed of the same amino acid sequence as native human pituitary GH, while somapacitan has a single-substitution modification that enables it to bind to albumin. Both somapacitan and lonapegsomatropin can be used in treatment-naïve or treatment experienced individuals and may be a useful option in those who have trouble adhering to daily injections. Recombinant GH formulations must be administered by intramuscular or subcutaneous injection. Nutropin AQ, Norditropin, and Omnitrope do not require reconstitution, while the remaining products are formulated as lyophilized powders for injection, and patients must be instructed regarding proper administration. Needle-free injection devices are available for use, which may be useful for patients who experience significant fear of injections. The potency of GH products is expressed as international units per milligram (international units/mg), with 1 mg containing approximately 2.6 international units of GH. Direct comparisons between the different recombinant GH products have not been published. However, all GH products are generally considered to be equally effective, and some retrospective data suggest that switching formulations during the course of treatment does not negatively impact growth trajectory.[62] The recommended initial dose for GHD in children is 0.16 to 0.24 mg/kg/week[49] (strong recommendation, low-quality evidence). In contrast, initial dosing in adult GHD is often fixed, with lower doses recommended for patients over 60 years (100-200 mcg/day) compared to patients 30 to 60 years (200-300 mcg/day) and under 30 years (400-500 mcg/day).[50] Recombinant GH can be administered daily or in equal doses six times per week, depending on the specific GH product used.[47,51] Dosing regimens with

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greater frequency of administration have been shown to provide more favorable short-term growth responses.[49] While fixed-dose strategies have historically been used, most endocrinologists suggest that adjustments in GH replacement can be made based on IGF-1 serum concentrations based on the patient's age and sex.[63,64] GH replacement therapy should be initiated as early as possible after a diagnosis of GH insufficiency and continued until a desirable height is reached or growth velocity has decreased to less than 2.5 cm per year after the pubertal growth spurt. However, the suitable time point for discontinuation of therapy with growth-promoting doses remains controversial. The Pediatric Endocrine Society recommends treatment be given until the growth velocity slows to below 2 to 2.5 cm/year[49](strong recommendation, low-quality evidence). Glucocorticoids may inhibit the growth-promoting effects of recombinant GH, and concomitant administration of androgens, estrogens, thyroid hormones, or anabolic steroids may accelerate epiphyseal closure and compromise final height.

Large databases, such as the National Cooperative Growth Study (NCGS), the Kabi International Growth Study (KIGS), and the Australian and New Zealand growth database (OZGROW), have been developed to collect post-marketing adverse event data associated with recombinant GH. These databases are organized and maintained by pharmaceutical companies that manufacture GH products.[65–67] Results from the Safety and Appropriateness of Growth Hormone treatments in Europe (SAGhE) study provide additional long-term surveillance data from a noncommercial source.[67] Recombinant GH is generally well-tolerated in children, and adverse effects are relatively uncommon.[51,65–68] A small number of patients may complain of injection-site pain or arthralgias. Idiopathic intracranial hypertension, also known as *pseudotumor cerebri*, has been reported in a very small number of children receiving GH therapy. This condition usually develops within the first 8 to 12 weeks of treatment and presents with symptoms such as headache, blurred vision, diplopia, nausea, and vomiting.[51] The symptoms of idiopathic intracranial hypertension usually resolve after discontinuation of GH therapy, and long-term complications are rare. Cases of slipped capital femoral epiphysis have been reported in children with GHD who are receiving GH therapy.[51,67,68] This condition is thought to occur as a result of the increased width of the femoral plate during GH treatment, but it also has been reported in GHD children who are not receiving GH replacement. Patients with this condition typically complain of hip or knee pain. Slipped capital femoral epiphysis can be managed by an orthopedic surgeon, and GH therapy does not need to be discontinued. Because GH is known to cause decreased insulin sensitivity, hyperglycemia and diabetes mellitus may develop.[68] Patients who have specific predisposing risk factors for diabetes mellitus are at greatest risk for this adverse effect.[65,68] Glycosylated hemoglobin concentrations should be monitored in all patients receiving GH products.[47] GH could theoretically promote the growth of various types of neoplasms and increase tumor recurrence rates in patients with a history of malignancy.[47,65,68] Consensus statements for professional organizations recommend that GH can be safely used in those without a history of malignancy but note that current evidence is insufficient to conclude whether GH increases cancer risk or recurrence.[51,69] In 1988, a Japanese report indicated that children receiving GH therapy were twice as likely to develop leukemia as children who were not receiving the hormone. A more recent analysis of all collected reports of leukemia associated with GH therapy determined that these children had other leukemia risk factors (Fanconi anemia, Bloom syndrome, or history of cancer).[67] GH therapy in children without these risk factors does not appear to predispose children to develop leukemia.[51,67,69] Concerns have been raised from the SAGhE cohort about the possibility that childhood GH exposure may be associated with diseases that may not manifest until adulthood. Increased cardiac and cerebrovascular mortality rates were observed in adult French subjects treated with GH therapy as children, but similar results were not seen in subjects from Belgium, the Netherlands, and Sweden.[67,70] The observational design of these studies makes interpretation of the findings difficult. Additionally, it should be noted that some authors have stressed the importance of using growth velocity and provocative testing in deciding whom and when to treat, and at what doses.

#### Recombinant Insulin-Like Growth Factor-1

Recombinant IGF-1 (mecasermin [Increlex]) is approved by the FDA for the treatment of children with short stature due to severe primary IGF-1 deficiency (defined as children with height standard deviation score ≤–3.0 plus basal IGF-1 standard deviation score ≤–3.0, plus normal or elevated GH concentration) or GH gene deletion with neutralizing antibodies to GH. Recombinant IGF-1 products are not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of glucocorticoids. Recombinant IGF-1 products have been shown to increase growth velocity in children with short stature who have low IGF-1 serum concentrations and resistance to GH.[71–73] However, the efficacy of these agents is less than that reported with GH products in patients with GH deficiency.

The recommended dose of mecasermin is 0.04 to 0.12 mg/kg administered by subcutaneous injection twice daily. First-year growth and long-term outcomes are best with doses more than 0.1 mg/kg/dose, adjusted for increases in weight as the patient grows. Treatment continues until epiphyseal

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closure or attainment of full growth potential.[71,72] Because of the insulin-like effects of these products, patients should be monitored very closely for hypoglycemia, and the drug should be initiated at the lower end of the dosage range and administered with a meal or snack. Additional adverse effects experienced by patients receiving recombinant IGF-1 products include injection-site reactions, tonsillar/adenoidal hypertrophy, lymphoid hypertrophy, coarsening facial features, anaphylaxis, headache, dizziness, and arthralgia.[71–73] Intracranial hypertension has been reported in a small number of patients. Additional studies are needed to elucidate the role of recombinant IGF-1 products in the management of short stature not caused by GH gene deletion or GH receptor defects.

### Evaluation of Therapeutic Outcomes

The large number of GHD disorders vary in their phenotype as well as biochemical and molecular characteristics. This likely explains the significant variability in the response observed in clinical trials with GH or IGF-1. Given this variability, and in the absence of specific and well-validated indicators of response, therapy must be individualized.[74] Appropriate monitoring of therapy for GHD and non-GHD short stature includes regular assessments of height, weight, growth velocity, serum IGF-1 concentrations, and bone age every 6 to 12 months. Additional laboratory tests to monitor for potential adverse effects include serum glucose concentration and thyroid function. The dose of GH should be periodically increased as weight increases in growing children.

### Conclusion

GH deficiency during childhood results in short stature. Replacement with recombinant GH is the drug of choice for patients with GHD short stature, but its use for the treatment of non-GHD short stature remains controversial despite FDA approval for this indication. Recombinant GH has proven to be safe for use in children and is associated with few adverse effects. Preparations of IGF-1 may provide benefit for patients with non-GHD short stature. GH regimens can be particularly demanding and inconvenient for pediatric patients because they must be administered by subcutaneous injection.

## HYPERPROLACTINEMIA

Prolactin is secreted in a pulsatile fashion by the lactotroph cells of the anterior pituitary, with the highest concentrations observed during sleep.[4] The secretion of prolactin is primarily regulated by the inhibitory effects of dopamine from the hypothalamus. Many factors can effect prolactin secretion (see Table e98-1). During pregnancy, prolactin serum concentrations substantially rise. All other conditions characterized by excess prolactin serum concentrations, known as *hyperprolactinemia*, are considered pathologic. Hyperprolactinemia is a state of persistent serum prolactin elevation. In the absence of stress, a prolactin serum concentration above the normal range (25 mcg/L ([1,090 pmol/L]) is generally considered indicative of hyperprolactinemia.[75] Hyperprolactinemia usually affects women of reproductive age.[75,76] The annual incidence of hyperprolactinemia in women between the ages of 25 and 34 years is approximately 24 cases per 1,000 person-years.[75]

Hyperprolactinemia has several etiologies. The most common causes are benign prolactin-secreting pituitary tumors, known as *prolactinomas*, and medications. Prolactinomas are classified based on size. Prolactin-secreting microadenomas are less than 10 mm in diameter and typically do not increase in size.[77] In contrast, macroadenomas are tumors with a diameter greater than 10 mm that continue to grow and can cause invasion of surrounding tissues.[4] In the presence of a prolactinoma, the elevation in prolactin serum concentration is generally proportional to the size of the tumor, with prolactin concentrations more than 500 mcg/L (22,000 pmol/L) typically diagnostic for a macroprolactinoma.[75–77]

7 Any pharmacologic agent that antagonizes dopamine or increases the release of prolactin can induce hyperprolactinemia (Table e98-4).[78] Antipsychotic medications are the most frequently reported agents to cause hyperprolactinemia due to their potent dopamine-receptor blockade. Serotonin is a strong stimulator of prolactin secretion and antidepressants such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors, tricyclic, and tetracyclic agents are associated with hyperprolactinemia.[78] The $5HT_1$ receptor agonist eletriptan has also been implicated as a potential cause of hyperprolactinemia.[79] Metoclopramide and domperidone, an antiemetic available in Europe, are potent dopamine-receptor antagonists reported to induce hyperprolactinemia.[78] Hormones such as estrogen and progesterone, commonly prescribed as oral contraceptives, can stimulate lactotroph growth to promote prolactin secretion and have been implicated in drug-induced hyperprolactinemia. Although the exact mechanism of action remains to be determined, the calcium channel-blocking agent verapamil has been associated with cases of

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hyperprolactinemia.[4,78] Methyldopa and reserpine, although not frequently used today, are antihypertensive agents that can stimulate prolactin secretion.[78] Prolactin concentrations may increase with the administration of GnRH agonists such as leuprolide or goserelin.[78] Other medications rarely reported to cause hyperprolactinemia include $H_2$-receptor blocking agents, benzodiazepines, opioids, and protease inhibitors.[4,78] Prolactin levels do not typically rise to more than 150 mcg/L (6,500 pmol/L) in most cases of drug-induced hyperprolactinemia. Measurement of serum prolactin concentrations prior to the initiation of therapy with medications known to cause hyperprolactinemia may obviate the need for extensive examination of pituitary function and aid the diagnosis of drug-induced causes.

TABLE e98-4

**Drug-Induced Hyperprolactinemia**

**Dopamine antagonists**

- Antipsychotics
- Phenothiazines
- Metoclopramide
- Domperidone

**Prolactin stimulators**

- Methyldopa
- Reserpine
- SSRIs
- $5HT_1$ receptor agonists
- Estrogens
- Progestins
- Protease inhibitors
- GnRH analogs
- Benzodiazepines
- Tricyclic and tetracyclic antidepressants
- MAO inhibitors
- $H_2$-receptor antagonists
- Opioids
- Cocaine

**Other**

- Verapamil

*Data from References [76–78].*

Less common etiologies of hyperprolactinemia include CNS lesions that physically compress the pituitary stalk and interrupt hypothalamic dopamine secretion.[75] Increased TRH concentrations in hypothyroidism can stimulate prolactin secretion and cause hyperprolactinemia. During conditions of renal or hepatic compromise, the clearance of prolactin is decreased, resulting in elevated prolactin concentrations.[75] Mutation of the prolactin receptor has also been identified as a cause of hyperprolactinemia.[76] Despite a rigorous diagnostic workup, the cause of hyperprolactinemia cannot always be determined. In such cases, the condition is referred to as *idiopathic hyperprolactinemia*.[75,76] It should be noted that many physiologic factors, such as stress (including the stress of phlebotomy), sleep, exercise, coitus, and eating, can induce transiently elevated prolactin levels.[4] Therefore, some clinicians may prefer obtaining multiple prolactin measurements to confirm the diagnosis.[75] Ideally, after an IV line is placed in the patient's arm, the patient should rest in a supine position or in a chair for 2 hours before prolactin samples are collected.

Elevated prolactin serum concentrations inhibit gonadotropin secretion and sex-steroid synthesis. Because prolactin concentrations greater than 60

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mcg/L (2,600 pmol/L) are associated with anovulation, women with hyperprolactinemia typically present with menstrual irregularities such as oligomenorrhea or amenorrhea and infertility.[75] In addition, approximately 40% to 80% of women with hyperprolactinemia will have galactorrhea.[75,77] The clinical presentation of patients with hyperprolactinemia is summarized in Table e98-5.[4,75–77]

TABLE e98-5

**Clinical Presentation of Hyperprolactinemia**

**General**

- Hyperprolactinemia most commonly affects women and is rare in men.

**Signs and symptoms**

- The patient may complain of symptoms related to local effects of the prolactin-secreting tumor, such as headache and visual disturbances that result from tumor compression of the optic chiasm.
- Female patients experience oligomenorrhea, amenorrhea, galactorrhea, infertility, decreased libido, hirsutism, and acne.
- Male patients experience decreased libido, erectile dysfunction, infertility, reduced muscle mass, galactorrhea, and gynecomastia.

**Laboratory tests**

- Prolactin serum concentrations at rest will be more than 25 mcg/L (1,090 pmol/L).

**Additional clinical sequelae**

- Prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to decreased bone mineral density and osteoporosis.
- The risk for ischemic heart disease may be increased with untreated hyperprolactinemia.

*Data from References* [4,75,77].

The diagnosis of hyperprolactinemia, which requires a single prolactin serum concentration greater than 25 mcg/L (1,090 pmol/L), is relatively simple.[75] However, identifying the underlying cause is often challenging. Patients with modest prolactin elevations should have multiple prolactin serum determinations to eliminate transient increases in prolactin as the culprit. A careful medication history is essential, and the presence of hypothyroidism, renal failure, or hepatic dysfunction should be evaluated. If the cause of hyperprolactinemia remains ambiguous, a computed tomography scan or MRI study should be performed to determine the presence of a pituitary tumor.[75,77] If an underlying cause cannot be determined, the hyperprolactinemia is considered to be idiopathic. Prolactin serum concentrations may appear falsely elevated in the presence of macroprolactin, a large polymeric form of prolactin with negligible biological activity. Testing for the presence of macroprolactin is recommended for asymptomatic patients who have elevated prolactin serum concentrations.[75]

## Treatment

The treatment of hyperprolactinemia should be directed toward the underlying cause. Treatment options for the management of prolactinomas include clinical observation, medical therapy with dopamine agonists, radiation therapy, and transsphenoidal surgical removal of the tumor.[4,75–77] Sex-steroid replacement should also be considered when clinically indicated.[75]

In cases of drug-induced hyperprolactinemia, discontinuation of the offending medication and initiation of an appropriate therapeutic alternative most often will normalize serum prolactin concentrations.[78] Aripiprazole, an atypical antipsychotic with partial dopamine $D_2$-receptor agonist activity, appears effective for managing antipsychotic-induced hyperprolactinemia as an adjunctive therapy and a therapeutic alternative when patients have been switched from an offending antipsychotic agent.[80] Metformin may also be useful for the management of antipsychotic-induced hyperprolactinemia.[81] In cases for which an appropriate therapeutic alternative does not exist, medical therapy with bromocriptine or cabergoline may be carefully considered (The Endocrine Society; weak recommendation with very low-quality evidence).[75]

Because prolactin-secreting microadenomas are very small and typically do not increase in size, treatment of these tumors is primarily directed toward

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alleviating symptoms.[75–77] The goal of therapy is to normalize prolactin serum concentrations and reestablish gonadotropin secretion to restore fertility and reduce the risk of osteoporosis. In patients with asymptomatic elevations in serum prolactin, observation and close follow-up are appropriate.[75] For women with amenorrhea who do not wish to become pregnant, dopamine agonist therapy may not be necessary. In these patients, sex hormone replacement and close follow-up may be sufficient.[75] Treatment goals are more aggressive in patients with prolactin-secreting macroadenomas because these tumors are larger and can cause invasion of local tissues and visual defects. Therefore, in addition to normalizing prolactin concentrations, tumor shrinkage and correction of visual defects are the primary goals of treatment.

Medical therapy with dopamine agonists usually is more effective than transsphenoidal surgery for both micro- and macro-prolactinomas.[4,75–77] Postsurgical cure rates depend on tumor type and the expertise of the neurosurgeon. Long-term cure rates are approximately 75% for microprolactinomas but only 34% for macroprolactinomas.[76] Transsphenoidal surgery for removal of prolactinomas is reserved for patients who are refractory to or cannot tolerate therapy with dopamine agonists and for patients with very large tumors that cause compression of adjacent tissues.[4,75–77] Radiation therapy may require several years for effective tumor shrinkage and reduction in serum prolactin concentrations. Thus, radiation therapy is reserved for patients with treatment-resistant macroprolactinomas.[77]

## Pharmacologic Therapy

Medical therapy with dopamine agonists is very effective in normalizing prolactin serum concentrations, restoring gonadal function, and reducing tumor size. The Endocrine Society Clinical Practice Guidelines recommend treatment with dopamine agonists as first-line therapy (strong recommendation with high-quality evidence).[75] Cabergoline, a long-acting dopamine agonist that can be dosed less frequently, is considered the drug of choice for the medical management of prolactinomas because of its superior efficacy when compared to bromocriptine (strong recommendation with high-quality evidence).[75]

### Bromocriptine

Bromocriptine, a $D_2$-receptor agonist, was commonly used in the treatment of hyperprolactinemia for more than 40 years.[82] It inhibits the release of prolactin by directly stimulating postsynaptic dopamine receptors in the hypothalamus. Hypothalamic release of dopamine (prolactin-inhibitory hormone) inhibits the release of prolactin. Decreases in serum prolactin concentrations occur within 2 hours of oral administration, with maximal suppression occurring after 8 hours. Prolactin suppression persists for up to 24 hours. Medical therapy with bromocriptine normalizes prolactin serum concentrations, restores gonadotropin production, and shrinks tumor size in approximately 80% of patients with microprolactinomas and 70% of patients with macroprolactinomas.[76]

For the management of hyperprolactinemia, bromocriptine therapy typically is initiated at a dose of 1.25 to 2.5 mg once daily at bedtime to minimize adverse effects.[4] The dose can be gradually increased by 1.25-mg increments every week to obtain desirable serum prolactin concentrations. Usual therapeutic doses of bromocriptine range from 2.5 to 15 mg/day, although some patients may require doses as high as 40 mg/day. Bromocriptine usually is administered in two or three divided doses, but once-daily dosing is also effective.[76]

The most common adverse effects associated with bromocriptine therapy include CNS symptoms such as headache, lightheadedness, dizziness, nervousness, and fatigue. GI effects such as nausea, abdominal pain, and diarrhea also are common. Bromocriptine should be administered with food and titrated slowly to decrease the incidence of adverse GI effects. Although most of these adverse effects diminish with continued treatment, approximately 12% of patients discontinue bromocriptine therapy due to adverse effects. Vaginal preparations of bromocriptine may be used in women to decrease the incidence of adverse effects associated with oral adminstration.[4,75]

Many patients with hyperprolactinemia are women with a principal complaint of infertility. Thus, the safety of bromocriptine in pregnancy must be considered. More than 6,000 pregnancies have been reported in women who received bromocriptine during pregnancy. The risk of spontaneous abortion or congenital anomalies does not appear to be increased.[75] Despite these data, discontinuation of therapy as soon as pregnancy is detected is recommended because the effects of in utero exposure to bromocriptine on gonadal function and fertility of the offspring remain unknown (The Endocrine Society; strong recommendation with low-quality evidence).[4,75,82] In patients with macroprolactinomas with rapid tumor expansion, bromocriptine therapy may need to be continued throughout pregnancy (The Endocrine Society; weak recommendation with low-quality evidence).

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### Cabergoline

Cabergoline is a long-acting dopamine agonist with high selectivity and affinity for dopamine $D_2$-receptors. Cabergoline effectively reduces serum prolactin concentrations and tumor size in patients with both microprolactinomas and macroprolactinomas.[75] Compared to bromocriptine, cabergoline is significantly more effective.[76,82] A systematic review and meta-analysis of four clinical trials comparing the efficacy of cabergoline and bromocriptine reported that cabergoline was significantly more effective in normalizing serum prolactin concentrations.[82] Cabergoline has also proved effective in patients who are intolerant of or resistant to bromocriptine and is as effective in men as in women with microprolactinomas and macroprolactinomas.[75]

Cabergoline is commercially available as 0.5-mg oral tablets. The initial dose of cabergoline for treatment of hyperprolactinemia is 0.25 to 0.5 mg once weekly or in divided doses twice weekly. This dose may be increased by 0.5-mg increments at 4-week intervals based on serum prolactin concentrations.[83] The usual effective dose is 0.5 to 1 mg weekly; doses more than 3.5 mg per week are rarely required.[76] However, doses as high as 12 mg weekly have been used safely in patients with treatment-resistant prolactinomas.[83] Following oral administration, peak serum concentrations are obtained within 2 hours, and food does not affect absorption. The elimination of cabergoline from the pituitary appears to be very slow; this may explain the long duration of action. Cabergoline is extensively metabolized in the liver by hydrolysis, and the dose should be reduced in patients with severe hepatic failure.

The most common adverse effects reported with use of cabergoline are nausea, vomiting, headache, nasal congestion, and dizziness.[77,82] These effects are similar to the adverse effects reported with bromocriptine. However, in a large comparative study evaluating bromocriptine and cabergoline, fewer patients receiving cabergoline reported adverse effects than did patients receiving bromocriptine. Only 3% of the patients in the cabergoline group withdrew from the study because of adverse effects versus 12% of patients taking bromocriptine.[84] Other adverse events associated with the use of cabergoline include mood disorders, exacerbation of existing psychosis, and poor impulse control.[76,77] As with other dopamine agonists, adverse events usually occur early in therapy and subside with continued use. A reduction in blood pressure has been observed in up to 50% of patients taking cabergoline; however, the incidence of symptomatic orthostatic hypotension has not been significant.[82,84] Transient increases in serum alkaline phosphatase, bilirubin, and aminotransferases have been reported in small numbers of patients receiving cabergoline.[84] Newly diagnosed cardiac valve regurgitation has been reported with cabergoline used in larger doses for the treatment of Parkinson disease.[76] Symptomatic cardiac valve abnormalities have not been observed with doses used for the treatment of prolactinomas.[76,77] However, data from one meta-analysis suggests a potential association between low-dose cabergoline and asymptomatic tricuspid regurgitation in patients treated for hyperprolactinemia.[85] Therefore, some clinicians recommend a baseline and routine follow-up echocardiography for patients receiving long-term cabergoline treatment for prolactinomas, especially if the dose exceeds 2 mg/week.[86]

Cabergoline use during pregnancy has not been extensively studied. Several case reports of women who received cabergoline therapy during the first and second trimesters of pregnancy have not documented an increased risk of spontaneous abortion, congenital abnormalities, or tubal pregnancy.[87] However, prospective data in large numbers of pregnancies are lacking. Because of the long half-life and limited data on cabergoline use in pregnancy, current guidelines recommend that women receiving cabergoline therapy who plan to become pregnant should discontinue the medication as soon as pregnancy is detected (The Endocrine Society; strong recommendation with low-quality evidence).[75]

Quinagolide, a $D_2$-receptor agonist used frequently in Europe, is dosed once daily. Quinagolide has been shown to be as effective as bromocriptine for the management of hyperprolactinemia and may be effective in the treatment of patients who are resistant to or intolerant of bromocriptine.[4]

## Evaluation of Therapeutic Outcomes

Prolactin serum concentrations should be monitored every 3 to 4 weeks after the initiation of any dopamine-agonist therapy to assess the efficacy and appropriately titrate the dose.[75] Symptoms such as headache, visual disturbances, menstrual cycles in women, and sexual function in men should be evaluated to assess response to therapy. Once prolactin concentrations have normalized and symptoms have resolved with dopamine-agonist therapy, prolactin serum concentrations should be monitored every 6 to 12 months. In patients who have received medical therapy with a dopamine agonist for at least 2 years, therapy may be tapered or discontinued if normal serum prolactin concentrations are achieved in the absence of visible

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tumor (The Endocrine Society; weak recommendation with low-quality evidence).[75] Follow-up of such patients should include prolactin serum concentration measurements every 3 months for the first year (continued annually thereafter) with an assessment of MRI findings if prolactin concentrations are elevated.

### Conclusion

Hyperprolactinemia is a common disorder that can have a significant impact on fertility. Hyperprolactinemia is most commonly caused by the presence of prolactin-secreting pituitary tumors and medications that antagonize dopamine or increase the secretion of prolactin. Available treatment options for this disorder include medical therapy with dopamine agonists, radiation therapy, and transsphenoidal surgery. In most cases, medical therapy with dopamine agonists is considered the most effective treatment. Cabergoline is the drug of choice because it is better tolerated and more effective than bromocriptine.

## PANHYPOPITUITARISM

10 Panhypopituitarism is a condition of complete or partial loss of both anterior and posterior pituitary function resulting in multiple pituitary hormone deficiencies. Patients with panhypopituitarism may have ACTH deficiency, gonadotropin deficiency, GH deficiency, hypothyroidism, and hyperprolactinemia. Panhypopituitarism is classified as either primary or secondary based on the etiology. Primary panhypopituitarism involves an abnormality within the secretory cells of the pituitary. Secondary panhypopituitarism is caused by a lack of proper external stimulation needed for the normal release of pituitary hormones. Some of the most common causes of panhypopituitarism include pituitary tumors, ischemic necrosis of the pituitary, surgical trauma, irradiation, and CNS infections. Pharmacologic treatment of panhypopituitarism is essential and consists of the replacement of pituitary hormones to address specific deficiencies. Replacement most often consists of glucocorticoids, thyroid hormone preparations, and sex steroids. Administration of recombinant GH also may be necessary. Patients with panhypopituitarism will need lifelong replacement therapy and close monitoring of multiple homeostatic functions.

## ABBREVIATIONS

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| | |
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| AACE | American Association of Clinical Endocrinologists |
| ACTH | adrenocorticotropic hormone |
| CNS | central nervous system |
| CRH | corticotropin-releasing hormone |
| FSH | follicle-stimulating hormone |
| GEP-NETs | gastroenteropancreatic neuroendocrine tumors |
| GH | growth hormone |
| GHD | growth hormone deficiency/growth hormone–deficient) |
| GHRH | growth hormone-releasing hormone |
| GI | gastrointestinal |
| GnRH | gonadotropin-releasing hormone |
| IGF | insulin-like growth factor |
| IGFBP-3 | insulin-like growth factor-1 binding protein-3 |
| LH | luteinizing hormone |
| MAO | monoamine oxidase |
| MRI | magnetic resonance imaging |
| OGTT | oral glucose tolerance test |
| SAGhE | Safety and Appropriateness of Growth Hormone treatments in Europe |
| SGA | small for gestational age |
| SHOX | short stature homeobox gene |
| SSRI | selective serotonin reuptake inhibitor |
| TRH | thyrotropin-releasing hormone |
| TSH | thyroid-stimulating hormone |
| VIP | vasoactive intestinal peptide |

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## SELF-ASSESSMENT QUESTIONS

1. Which of the following physiologic functions is *not* regulated by anterior pituitary hormones?

   A. Growth

   B. Thyroid function

   C. Ovulation

   D. Uterine contraction

2. Which of the following clinical characteristics is common to acromegalic patients?

   A. Diarrhea

   B. Increased shoe size

   C. Weight loss

   D. Alopecia

3. The preferred initial treatment option for a patient recently diagnosed with acromegaly is:

   A. Bromocriptine.

   B. Lanreotide.

   C. Transsphenoidal surgery.

   D. Radiation therapy.

4. KL is a 58-year-old man who was recently diagnosed with acromegaly. His past medical history is significant for type 2 diabetes and obesity. He is currently complaining of fatigue, joint pain, increased sweating, and headaches. He is not a candidate for transphenoidal surgery. Which of the following treatments is most appropriate for first-line treatment of KL's symptoms?

   A. Bromocriptine

   B. Cabergoline

   C. Octreotide

   D. Radiation therapy

5. Which of the following information is most important to provide to a patient with a new prescription for lanreotide?

   A. Concomitant therapy with ursodeoxycholic acid is needed to prevent gallstones.

   B. The most common adverse effect of lanreotide therapy is headache.

   C. A standard multiple vitamin is recommended during therapy.

   D. GI adverse effects should subside within 10 to 14 days of therapy.

6. Which of the following clinical characteristics is common to patients with GH-deficient short stature?

   A. Normal GH serum concentrations

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B. Physical height <2 standard deviations below the population mean

C. Malnutrition

D. Hyperglycemia

7. Which of the following assessments need to be considered for the diagnosis of GH deficiency?

A. Bone age and growth velocity

B. Random GH level

C. Serum glucose concentrations

D. Body weight

8. For which of the following conditions does recombinant human growth hormone therapy have a definitive role?

A. Chronic fatigue syndrome

B. GH-deficient short stature

C. Natural aging

D. Depression

9. Which of the following parameters should be monitored in a patient receiving recombinant human growth hormone therapy?

A. Prolactin

B. Menstrual cycles in women

C. Echocardiography

D. Insulin growth factor 1

10. Which of the following clinical characteristics is common in women with hyperprolactinemia?

A. Menstrual irregularities

B. Darkened skin

C. Dry mouth

D. Increased blood glucose

11. Which of the following classes of medications is most likely to cause drug-induced hyperprolactinemia?

A. β-blockers

B. Antidepressants

C. Antihistamines

D. Oral contraceptives

12. LJ is a 29-year-old woman who has been diagnosed with a prolactin-secreting adenoma that is 8 mm in diameter. She complains of amenorrhea for 1 year and galactorrhea from both breasts. Which of the following treatments is most appropriate for first-line treatment of LJ's symptoms?

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A. Radiation therapy

B. Transsphenoidal surgery

C. Dopamine agonist therapy

D. Somatostatin analog therapy

13. Which of the following dopamine agonists would be an appropriate choice for a patient with hyperprolactinemia who is trying to conceive?

A. Cabergoline

B. Ropinirole

C. Bromocriptine

D. Pramipexole

14. CM is a 30-year-old woman diagnosed with hyperprolactinemia. She recently began therapy with cabergoline. Which of the following adjunctive medications should be considered for CM?

A. Human growth hormone

B. Oral contraceptives

C. Multivitamins

D. Antacids

15. Which of the following treatments may be required for patients with panhypopituitarism?

A. Pasireotide

B. Cabergoline

C. Pegvisomant

D. Levothyroxine

## SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** See Table e98-1. The posterior pituitary gland is involved with uterine contraction via the secretion of oxytocin. The anterior pituitary gland is involved with growth via secretion of GH, thyroid function via secretion of TSH, and ovulation via secretion of LH/FSH. See the Anatomy and Physiology section for more information on pituitary gland regulation.

2. **B.** See Table e98-2 and clinical presentations of Acromegaly for more information. Increased shoe size is a sign that patients may exhibit.

3. **C.** Transsphenoidal surgery is considered for most patients unless the pituitary tumor is unresectable or the patient is a poor surgical candidate. See Treatment section of Growth Hormone Excess and Fig. e98-2 for more information on the approach to the treatment of acromegaly.

4. **C.** In patients who are poor candidates for surgery, somatostatin analogs, such as octreotide, are recommended primary therapy. See Somatostatin Analogs under Treatment section of Growth Hormone Excess and Fig. e98-2 for more information on the approach to the treatment of acromegaly

5. **D.** Prophylactic therapy for gallstones is not recommended as somatostatin-induced gallstones rarely present with symptoms. One of the first symptoms of acromegaly that may subside with somatostatin therapy is a headache. GI adverse effects of somatostatin analogs are seen in 75% of

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patients but usually subside within 10 to 14 days. See Somatostatin Analogs under Treatment section of Growth Hormone Excess for discussion on adverse effects

6. **B.** Patients will have a physical height greater than 2 standard deviations below the population mean for a given age and height. See Table e98-3 for the clinical presentation of short stature.

7. **A.** See Table e98-3 for laboratory tests commonly used for evaluation of GH deficiency. See GH deficiency section for discussion on presentation.

8. **B.** Growth hormone is indicated for GH-deficient short stature. See Recombinant Growth Hormone section discussion on indications and uses.

9. **D.** See Evaluation of Therapeutic Outcomes section under Growth Hormone Deficiency. Appropriate monitoring of therapy for efficacy includes regular assessments of height, weight, growth velocity, IGF-1, and bone age every 6 to 12 months in addition to glucose and thyroid function for monitoring adverse effects.

10. **A.** Menstrual irregularities. Women with hyperprolactinemia typically present with menstrual irregularities such as oligomenorrhea or amenorrhea because elevated prolactin concentrations inhibit gonadotropin secretion and sex-steroid synthesis. See Table e98-5 for more information about the clinical presentation of patients with hyperprolactinemia.

11. **B.** Antidepressants. SSRIs, MAO inhibitors, and tricyclic and tetracyclic agents are associated with hyperprolactinemia because serotonin is a strong stimulator of prolactin secretion. See Table e98-4 in the chapter for more information.

12. **C.** Dopamine agonist therapy. Medical therapy with dopamine agonists is usually more effective than transsphenoidal surgery and/or radiation for prolactin-secreting adenomas.

13. **C.** Bromocriptine. Information regarding the safety of dopamine agonists during pregnancy is more robust with bromocriptine. However, bromocriptine should be discontinued as soon as pregnancy is detected because the effects of in utero exposure to bromocriptine on gonadal function and fertility of the offspring remain unknown.

14. **B.** Oral contraceptives. Elevated prolactin concentrations inhibit gonadotropin secretion and sex-steroid synthesis. Therefore, sex-steroid replacement should be considered to reduce the risk of osteoporosis.

15. **D.** Panhypopituitarism results in complete or partial loss of anterior and posterior pituitary function. Therefore, pharmacologic treatment consists of replacement of specific pituitary hormones based on individual deficiencies.

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