Evaluating Hyperprolactinemia in Veterans

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Not all patients with elevated serum prolactin levels need to undergo expensive diagnostic imaging or therapeutic intervention. These clinicians present a systematic approach to diagnosis that helps practitioners manage each case appropriately.

Hyperprolactinemia, an abnormal elevation in serum prolactin levels, may occur secondary to a variety of etiologies, ranging from simple physiologic changes (such as an increase in stress) to serious illness (such as a large, hormone secreting pituitary mass). Given this extensive differential diagnosis, it is important for clinicians to identify the precise cause of hyperprolactinemia in a timely fashion so that the condition may be properly managed. Some patients, for instance, need prompt intervention and close follow-up, while others require no treatment and only periodic observation.

Accurately diagnosing the underlying cause of hyperprolactinemia may require multiple imaging studies as well as laboratory testing and physical examination. Not performing these tests when they are needed can result in misdiagnosis and, possibly, preventable patient morbidity. Such tests, however, are not always necessary and avoiding costly tests when appropriate not only saves money for the health care system but also spares the patient time consuming procedures that may cause unnecessary stress.

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While the degree to which prolactin levels are elevated provides an important clue to the etiology of the condition, it does not tell the entire story. In this article, we present a systematic approach for evaluating and managing hyperprolactinemia, with a special focus on veteran patients—in whom the finding of mildly elevated serum prolactin is fairly common.

THE PHYSIOLOGY OF PROLACTIN

Prolactin is a 198 amino acid polypeptide hormone secreted and stored in the lactotrophs of the pituitary gland. The lactotrophs comprise nearly 75% of all pituitary cells and are located predominantly in the peripheral portions of the gland. As a result, prolactin is resistant to destruction when the pituitary suffers from mass effect—usually because of a pituitary adenoma. In total, the pituitary contains about 100 µg of prolactin.

In contrast to other pituitary hormones, which respond to stimulatory peptides, prolactin is under tonic inhibition. The inhibitory peptide is dopamine (also known as prolactin inhibitory factor), and it is not affected by a specialized hypothalamic releasing factor. Histamine H1 receptor agonists also exert much weaker inhibition, and stimulants include estrogen, thyrotropin-releasing hormone (TRH), serotonin, gamma-aminobutyric acid, opiates, and histamine H2 receptor agonists.

Prolactin is secreted in a diurnal cycle of several pulses a day, mostly during the early morning hours of sleep. Prolactin's only known physiologic function is stimulation of milk production for breast feeding (in the presence of estrogen priming), but other physiologic stimuli may cause temporary elevations that are not considered pathologic (Table 1).

Pseudohyperprolactinemia

Prolactin ordinarily circulates in the serum in the active monomeric form, but small amounts can exist as dimers and polymers. Compared with prolactin, these macroprolactins have decreased receptor binding, biological activity, and clearance from the serum. As a result, accumulation in the serum leads to so-called "pseudohyperprolactinemia." This condition cannot be differentiated from true hyperprolactinemia by clinical features alone, can produce any degree of prolactin elevation, and may be associated with normal reproductive function or with hypogonadism.

Since patients with pseudohyperprolactinemia and normal reproductive function seldom require therapy, identifying such patients can prevent unnecessary imaging and treatment with dopamine agonists. This can be accomplished by screening hyperprolactinemic serum samples for macroprolactin complexes, using polyethylene glycol precipitation, prior to immunoassay. At one hospital in Dublin, Ireland, clinicians determined that macroprolactinemia accounted for 22% of such samples.[1]

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Table 1. Physiologic causes of elevated serum prolactin levels

- Dehydration
- Estrogen
- Exercise
- Food ingestion
- General anesthesia
- Hypoglycemia
- Menstrual cycle, luteal phase
- Nipple stimulation or intercourse
- Pregnancy or postpartum
- Sleep
- Stress
- Suckling

Prolactin also may combine with immunoglobulin G or nonimmunoglobulin G autoantibodies to form macroprolactins. New immunometric "sandwich" assays are being evaluated to further describe and quantitate these macroprolactins.[2]

The hook effect

When prolactin levels are markedly elevated, immunoassays may show deceptively low levels of the hormone because of a phenomenon called the "hook effect." This occurs when multiple prolactin molecules bind to a single antibody or carrier, generating a large molecular complex that is misinterpreted as a single prolactin molecule. Serial dilution of serum samples easily eliminates the hook effect, allowing for accurate assessment of prolactin levels. To prevent misdiagnosis, consider this procedure in all patients with large pituitary tumors and unexpectedly low prolactin levels (below 200 µg/L).[3]

VETERANS AND HYPERPROLACTINEMIA

Although hyperprolactinemia is most common in premenopausal women, it can affect both men and women of any age, and mild elevations of serum prolactin are found relatively frequently in veterans. One reason for this may be that the veteran population, which tends to be older and sicker than the general population, is prone to some of the most common causes of hyperprolactinemia, such as adverse drug reactions.

Aside from demographics, however, certain characteristics of military service may increase the likelihood of serum prolactin elevations in veterans. In addition to a well described relationship between acute stress (such as that caused by venipuncture) and temporary, nonpathologic prolactin elevations,[4] some research suggests a link between prolonged emotional stress and persistent hyperprolactinemia. In one case-controlled study, patients who developed sustained hyperprolactinemia reported significantly more life events in the previous year than did control patients.[5] Military personnel and veterans are subject to particular emotional stressors, including frequent relocation, family separation, and combat exposure. In some cases, these stressors have lasting effects, such as posttraumatic stress disorder (PTSD).

Furthermore, several studies indicate that stress experienced by veterans may influence physiologic—and perhaps pathologic—prolactin responses to other stimuli.[6–8] Grossman and colleagues found that the normal suppression of prolactin by low dose dexamethasone challenge was exaggerated in combat veterans (both those with and those without PTSD) compared with control patients.[6] By contrast, cortisol suppression was enhanced only in the group of combat veterans who had PTSD. These findings suggest that combat exposure alone may be sufficient to disrupt the normal prolactin response to dexamethasone. In other studies, the prolactin response to serotonergic agents was lower in veterans with PTSD[7] and was inversely associated with indexes of depression and hostility in alcoholic veterans enrolled in a rehabilitation program.[8]

EVALUATING HYPERPROLACTINEMIA

In the blood, prolactin levels are considered normal when they are lower than 15 µg/L in men and lower than 20 µg/L in women, taking into account individual laboratory variation. While a substantial number of hyperprolactinemia cases are asymptomatic and discovered incidentally, clinicians should suspect and test for the condition when any patient presents with erectile dysfunction, galactorrhea, infertility, or menstrual irregularities.

Pathologic hyperprolactinemia is defined as a prolactin level consistently greater than 20 µg/L, so multiple blood samples are needed to confirm the diagnosis. Since hyperprolactinemia persists throughout the day, blood can be drawn during the routine office visit. Be aware, however, that venipuncture alone can produce prolactin elevations of up to 50 µg/L, especially in women.[4] If the venipuncture sample is elevated, therefore, the test should be repeated, with the blood sample drawn through an indwelling catheter, without a tourniquet, and before a breast exam.

Mild prolactin elevations (20 to 50 µg/L) may result from a normal secretory pulse, a physiologic elevation, or an underlying abnormality requiring further investigation. Modest elevations (50 to 200 µg/L) may be associated with physiologic stimuli or a nonfunctioning or poorly functioning pituitary adenoma (a tumor that does not produce or produces only minute amounts of excess hormone). These tumors may or may not require treatment. Serum prolactin levels above 200 µg/L are almost

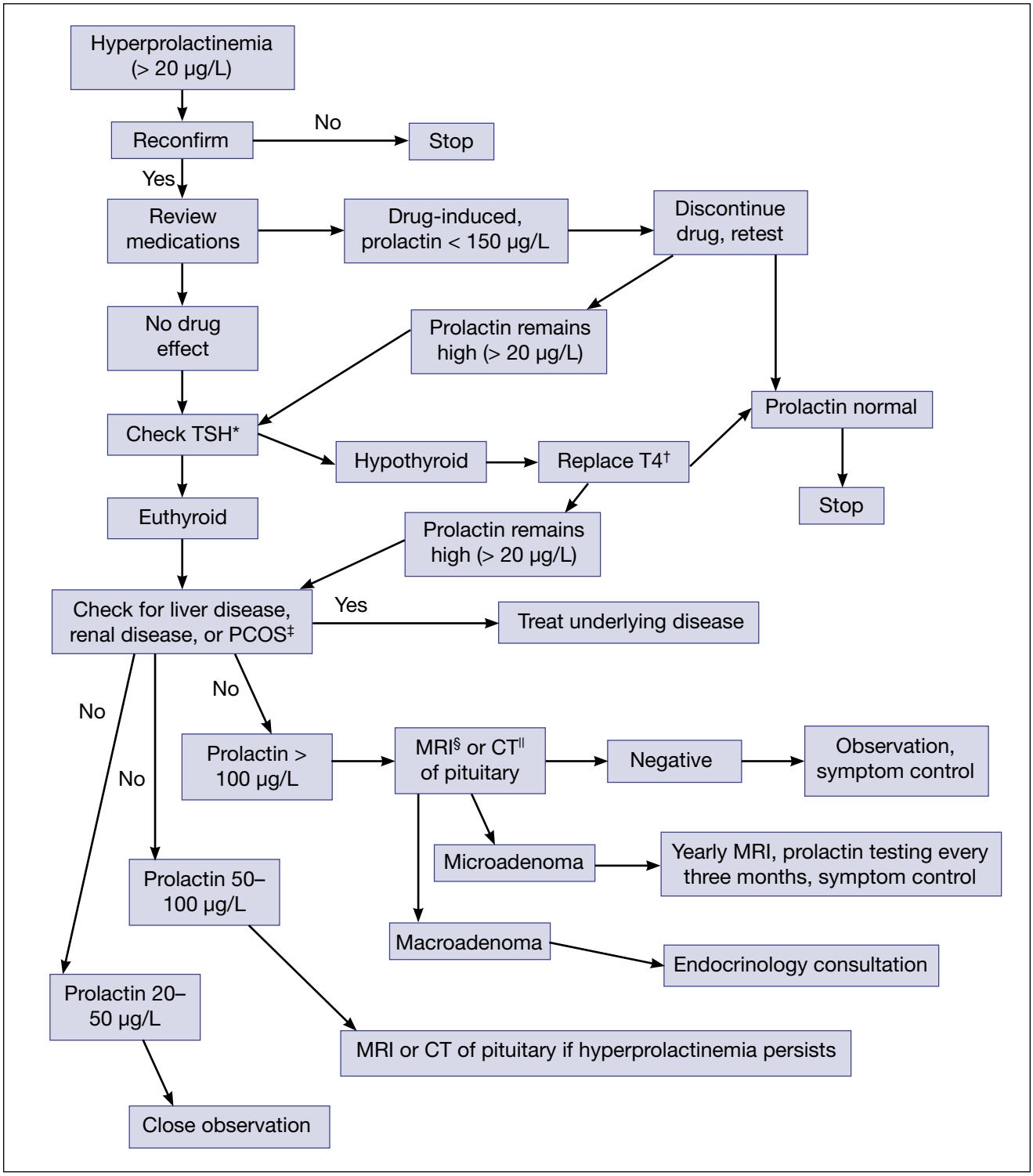

Figure. Algorithm for evaluating hyperprolactinemia in veterans. *TSH = thyroid stimulating hormone. †T4 = thyroxine. ‡PCOS = polycystic ovarian syndrome. §MRI = magnetic resonance imaging. ‖CT = computed tomography.

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always associated with the presence of a prolactinoma. In fact, this degree of hyperprolactinemia is, by itself, adequate to diagnose such a tumor.

Review the medication profile

At our VA medical center, drug-induced hyperprolactinemia accounts for 58% of endocrinology consultations for elevated prolactin. (S.L.Q., M.C.L.; unpublished data; February 2005). For this reason, we have found that a thorough review of the medication profile is the first, simplest, and most cost-efficient step in evaluating hyperprolactinemia (Figure). Many medications are known to raise serum prolactin, generally to mild or modestly elevated levels that remain below 150 µg/L (Table 2).[4]

When the etiology is questionable, it is prudent to discontinue the suspected drug temporarily and repeat the blood test to see if the prolactin level returns to normal. Once drug-induced hyperprolactinemia is confirmed, no further workup is needed.

Check thyroid function

If an adverse drug effect cannot sufficiently explain hyperprolactinemia, the next avenue to explore is thyroid dysfunction. While hypothyroidism is not a common cause of hyperprolactinemia, it is an easy culprit to identify and correct.

The hyperprolactinemia associated with hypothyroidism is believed to result from direct stimulation of prolactin by elevated levels of TRH. Generally, hyperprolactinemia occurs when thyroid-stimulating hormone (TSH) levels exceed 50 mIU/mL, and total thyroxine levels are below 2 µg/dL.[4] In more subtle cases, prolactin elevations may be absent unless induced by a TRH stimulation test, but as long as the patient's hypothyroidism has been recognized, there is no reason to perform this test. Restoration of euthyroidism corrects the hyperprolactinemia, but whether this occurs before or after normalization of TSH is controversial.[9–11]

In a recent study, Raber and colleagues found that hyperprolactinemia was not a common feature of hypothyroidism except in the presence of concomitant drug therapy with an agent known to elevate prolactin levels.[12] It is possible that the prolonged hyperprolactinemia associated with hypothyroidism in the past was related to profound elevations in TSH and delayed diagnosis. With the development of automated laboratory testing and an ultrasensitive TSH assay, this is no longer likely to occur.

Table 2. Medications or substances that can cause hyperprolactinemia

Dopamine receptor antagonists
- Phenothiazines
- Butyrophenones
- Metoclopramide

Dopamine depleting agents
- Methyldopa
- Reserpine

Antidepressants
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors

Others
- Cisapride
- Calcium channel blockers
- Estrogens
- Nicotine
- Cimetidine and other histamine H2 receptor blockers
- Opiates
- Domperidone
- Cocaine
- Gamma-aminobutyric acid
- Beer
- Monoamine oxidase inhibitors

Assess for renal, hepatic, and ovarian disease

Anywhere between 25% and 75% of patients with chronic renal failure have hyperprolactinemia in the 25- to 100-µg/L range.[13] In such cases, prolactin levels are not diminished by hemodialysis or peritoneal dialysis,[14–16] though they fall rapidly after transplantation.[17,18] Reduced prolactin clearance and altered neurotransmitter function are cited most often for the association between hyperprolactinemia and renal failure,[16] but increased prolactin synthesis also has been documented.[14]

Cirrhosis or hepatic failure and the polycystic ovarian syndrome (PCOS) also are associated with hyperprolactinemia—though to a lesser extent than chronic renal failure.[19] The mechanism of hyperprolactinemia in PCOS is not well described, but elevated prolactin and testosterone levels appear to be correlated.[20]

While women with PCOS are not unusually susceptible to osteoporosis, men with elevated prolactin levels have an increased incidence of osteopenia and osteoporosis because of hypogonadism and relatively unopposed estrogen activity.[21] Men with hyperprolactinemia, therefore, should have a screening bone densitometry test to evaluate bone mass, and men with hypogonadism who are receiving replacement testosterone treatment must be followed closely as aromatization of exogenous testosterone to estrogen may aggravate hyperprolactinemia.[22] In this situation, consider prescribing a nonaromatizable testosterone or using testosterone in conjunction with an aromatase inhibitor, such as anostrozole.

Rule out rare etiologies

Other uncommon causes of hyperprolactinemia include chest wall trauma or infection, HIV infection,

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adrenal insufficiency, and seizures. In patients with HIV infection, apparent hyperprolactinemia most often is actually pseudohyperprolactinemia caused by increased concentrations of macroprolactins and normal levels of monomeric prolactin.[23]

The exact mechanism of prolactin elevation in seizures is not well defined but may be related to the intense stress and physical activity associated with the seizure. In fact, some clinicians have used serum prolactin measurements to confirm true seizure activity,[24] rule out psychogenic seizures,[25] or differentiate types of seizures.[26] While not all sources agree on the clinical usefulness of this strategy,[25] the possibility of temporary postictal elevations in serum prolactin levels argues against evaluating patients for hyperprolactinemia immediately following a seizure.

Consider pituitary isolation syndrome or a prolactinoma

When other possible causes of hyperprolactinemia have been eliminated, suspicion should turn to a pituitary mass, which generally requires imaging studies to confirm. Any structural abnormality that impairs communication between the pituitary and hypothalamus can precipitate hyperprolactinemia by interrupting delivery of dopamine to the lactotrophs, resulting in elevated prolactin levels that usually do not exceed 200 µg/L. This situation, sometimes described as "pituitary isolation syndrome," can occur in the context of large, nonfunctioning pituitary adenomas; infiltrating diseases of the pituitary or hypothalamus; pituitary stalk section; empty sella syndrome; and arteriovenous malformations.

Distinguishing a true prolactinoma from a nonfunctioning tumor that is compressing the pituitary stalk is essential for establishing prognosis and proper treatment. Since the size of prolactinomas correlates well with serum prolactin levels, this is quite easy to do in the case of large prolactinomas, which are virtually the only cause of prolactin levels well above 200 µg/L. Smaller prolactinomas, however, are associated with lower prolactin levels that may overlap with those caused by nonfunctioning tumors.

Table 3. Evaluation of anterior pituitary function

Hormone	Screening test	Secondary test
GnRH*	LH,† FSH,‡ testosterone, estrogen, progesterone	GnRH stimulation test
GH§	Exercise, IGF‖-1	Insulin, arginine, dopamine, sleep, propranolol
TSH¶	Free T4,# T3**	TRH†† stimulation test
ACTH‡‡	ACTH stimulation test	ACTH, CRH,§§ insulin/hypoglycemia
Prolactin	Prolactin	TRH, insulin/hypoglycemia

*GnRH = gonadotropin-releasing hormone. †LH = luteinizing hormone. ‡FSH = follicle-stimulating hormone. §GH = growth hormone. ‖IGF = insulin-like growth factor. ¶TSH = thyroid-stimulating hormone. #T4 = thyroxine. **T3 = triiodothyronine. ††TRH = thyrotropin-releasing hormone. ‡‡ACTH = adrenocorticotropic hormone. §§CRH = corticotrophin-releasing hormone.

When the cause is unclear

When a precipitating cause has not been firmly established, the central nervous system must be evaluated by magnetic resonance imaging (MRI) or computed tomography (CT) scanning. MRI is preferred to evaluate soft or tumoral tissues, whereas CT scanning offers better definition of bony structures. CT is also useful when MRI is contraindicated.

MANAGING A PITUITARY MASS

Prolactinomas

Because menstrual irregularities are readily identifiable and galactorrhea is common, women with prolactinomas usually present earlier—with smaller tumors and lower serum prolactin levels—compared with men. Prolactinomas that are smaller than 10 mm are defined as microadenomas and sometimes can be managed with observation alone. Investigators who studied 30 patients with presumed microprolactinomas for five years observed progression in only six patients and spontaneous resolution in another six.[27] The remainder of the patients had no changes in tumor size or prolactin levels.[27] In another study, involving 41 patients with hyperprolactinemia but no demonstrable pituitary or central nervous system disease or other recognized cause, prolactin levels decreased or normalized during the follow-up period (up to 11 years; mean, 5.5 years) in 83% of the patients.[28]

In women with prolactinomas, normal menstrual function is most predictive of a favorable tumor course. Unfortunately, no equivalent predictive factor has been identified in men. Even when specific intervention is not indicated, clinicians should address symptoms and related morbidity (such as fertility issues, galactorrhea, and bone density) and perform serial MRIs every six to 12 months. Formal

testing of pituitary function is not required for microadenomas.

Macroadenomas, on the other hand, usually require treatment and evaluation for concomitant hormonal deficits (Table 3). The goal of therapy is to normalize prolactin secretion, alleviate symptoms, and reduce tumor size, so as to avoid damage to normal pituitary tissue and the optic chiasm.

Medical therapy with either bromocriptine or cabergoline is the mainstay of treatment for prolactinomas (Table 4). Both agents are rapid and effective dopamine agonists that decrease prolactin levels by directly inhibiting prolactin secretion. Bromocriptine is less expensive than cabergoline but more often causes nausea, vomiting, and central nervous system symptoms and must be taken daily. Cabergoline can be taken once or twice weekly. These drugs can reduce prolactin levels within days, though maximal response may take several months.

In general, prolactin levels and tumor size tend to be related. As long as levels are trending down, therefore, the tumor is unlikely to grow bigger. Often, even large tumors that produce visual field defects can be treated medically with close observation and serial visual field testing. The response rate of both microadenomas and macroadenomas to medical therapy appears to correlate with tumor size and ranges from 76% to 100%. It is sometimes possible to taper or discontinue therapy in patients who achieve normal prolactin levels and have no evidence of residual tumor on MRI—though other patients require a lifetime of suppressive therapy.[29]

Other therapeutic options include surgery and radiation therapy. Radiation can provide a definitive cure but works slowly and may result in panhypopituitarism. Surgery provides immediate results but is less likely than radiation to produce a cure. Postoperative prolactin levels are normal in 80% to 90% of patients, but tumor recurrence rates are high years later.[29] If the presurgical prolactin level is as high as 200 to 250 µg/L, surgical cures are possible in fewer than 30% of patients.[29] Patients who are most likely to require surgery are those who are nonadherent to or cannot tolerate medical therapy, those whose tumors are unresponsive to medication, and those who have pituitary apoplexy or persistent compression of the optic chiasm. Fortunately, such patients are few.

Table 4. Medical management of prolactinomas

Drug	Starting dosage	Maximum dosage	Adverse effects (% of patients)
Bromocriptine	1.25 mg/day	10 mg/day	• Nausea (50%) • Headache (20%) • Dizziness (20%)
Cabergoline	0.25 mg weekly	1 mg twice weekly	• Nausea (27%) • Constipation (5%)
Pergolide*	0.05 mg/day	5 mg/day	• Orthostasis (10%) • Dizziness (5%) • Gastrointestinal symptoms (5%)

*Approved by the FDA only for treatment of Parkinson disease but also effective in prolactinomas.

Nonprolactinomas

Large, nonfunctioning or poorly functioning pituitary adenomas that cause modest prolactin elevations of 100 to 200 µg/L because of pituitary stalk compression are sometimes mistaken for prolactinomas. When imaging reveals a large tumor, however, a prolactin level below 200 µg/L suggests that the tumor is nonfunctioning.

Medical therapy with bromocriptine or cabergoline lowers prolactin levels but does not affect the growth of nonprolactinomas. In a case in which a nonprolactinoma is mistaken for a prolactinoma, serial MRIs may be the only indication that medical therapy has failed. When this occurs, surgical resection or radiation therapy usually is the appropriate treatment, and these tumors must be followed closely. In rare cases in which macrodenomas appear to be stable, observation alone may be an acceptable management strategy.

SUMMING UP

The prevalence of hyperprolactinemia among veterans, its troubling symptoms, and the pituitary masses with which high levels of prolactin are associated suggest the importance of diagnosing and treating hyperprolactinemia in this population. An abnormally high prolactin level can range from a mild elevation of less than 50 µg/L to a profound elevation above 200 µg/L, which usually is associated with a prolactinoma. Elevated prolactin levels should be confirmed on multiple occasions. Evaluate persistently elevated levels greater than 100 µg/L with pituitary imaging, usually MRI. For prolactin levels greater than 50 µg/L but less than 100 µg/L and no obvious precipitating cause, also consider pituitary imaging. For stable prolactin levels below 50 µg/L, it may be acceptable

to follow serum levels for some time before considering pituitary imaging.

Treatment of hyperprolactinemia varies with the patient's symptoms and the size of the tumor. While prolactinomas larger than 10 mm usually require therapy, smaller tumors in asymptomatic patients may not require intervention. Medical management of prolactinomas with dopamine agonists usually is successful. A thorough review of the patient's history can identify potential etiologies for hyperprolactinemia that do not require radiologic evaluation or medical treatment at a considerable cost savings to the health care system.

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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