

Provision or Distribution of Growth Hormone for “Antiaging”

Clinical and Legal Issues

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THE DISTRIBUTION AND MARKETING OF HUMAN GROWTH hormone (HGH or GH) via Web sites and antiaging clinics has grown into a multimillion-dollar antiaging industry.¹⁻⁴ Despite congressional hearings warning of deceptive marketing claims and the potential health and economic dangers associated with the antiaging industry,^{5,6} and statements issued by the National Institute on Aging⁷⁻⁹ and the Federal Trade Commission,¹⁰ the distribution and use of GH for antiaging is now common. For example, entering the terms “HGH” and “anti-aging” into the Google search engine generated 3 410 000 hits as of September 26, 2005, many representing Web sites and clinics marketing and selling GH.

Worldwide annual sales of GH are estimated to be \$1.5 to \$2 billion.^{4,11} Vance¹² has suggested that 30% of GH prescriptions in the United States are for indications not approved by the Food and Drug Administration (FDA), which would include antiaging and athletic enhancement. In 2000, Langreth¹³ quoted an antiaging industry source as stating that 30 000 people were receiving injectible GH for antiaging at the time. United States officials reportedly estimated that 25 000 to 30 000 older individuals were treated with GH for antiaging in 2004.¹¹ In 2002, one antiaging clinic reported that one third of its 4000 patients were spending \$400 to \$500 per month for GH injections.¹¹

While precise figures on total GH distribution and use cannot be obtained, to estimate annual GH distribution in the United States, we contacted IMS Health (Fairfield, Conn), an independent pharmaceutical industry research company. IMS Health projects total national sales and prescription totals from a computerized panel of 22 000 retail pharmacies, including chain pharmacies, independents, mass merchandisers, and food store-based pharmacies, representing approximately 45% of the total prescription sales for the US retail market. IMS

Health also collects information from approximately 50 mail service outlets representing 70% of the US mail service market (Brian Palumbo, written communication, IMS Health, April 2005). Information from IMS Health indicates that a total of 212 921 new and refill GH prescriptions were filled by retail and mail service pharmacies in 2004 (Brian Palumbo, written communication, IMS Health, April 2005). These prescriptions generated total sales of approximately \$622 million (\$427 million via mail services and \$9.5 million via clinics), constituting 89% of sales for the class of drugs “anabolic hormones” (this class, for market surveillance purposes, includes GH) (Brian Palumbo, unpublished data, IMS Health, 2005). Of these GH prescriptions, 74% were for individuals aged 20 years and older and 43.7% were for individuals aged 40 to 59 years. These sales and prescription figures include legal prescribing for adult GH deficiency (GHD, defined below) and AIDS wasting syndrome, but do not include distribution of GH from antiaging Web sites. In 2002, physicians within the antiaging industry estimated that 100 000 individuals obtained the drug without a prescription.¹¹

Prescribing and administering GH has become a routine intervention¹⁴ in an industry that is variably called “antiaging,” “regenerative,” “longevity,” or “age-management” medicine, although not all physicians using these designations administer GH to their patients. A nonsystematic viewing of numerous Web sites revealed that the cost of pills and sprays allegedly containing GH is substantial, with both costing the consumer as much as \$200 to \$300 for what marketers indicate as a month’s supply (T.H.P., unpublished data, 2005). By contrast, the injectible form of GH typically costs from \$500 to \$1000 per month.¹³

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Clinical Effects of GH

Growth hormone has been documented to improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization,¹⁵ but without positive effects on strength, functional capacity, or metabolism.¹⁵⁻¹⁹ Furthermore, the positive effects may be short-lived: in a study of 148 patients with adult GHD (defined below), the modest beneficial effects on body composition (eg, 5% increase in lean body mass) disappeared for most individuals after 24 months of treatment, and 38% of study participants dropped out because of lack of subjective improvement.²⁰ In addition, the healthy lifestyle that patients who receive injectible GH are often encouraged to adopt, rather than the GH itself, may contribute to changes in body composition.

Growth hormone is associated with substantial adverse effects. In a clinical trial of healthy women (n=57) and men (n=74) aged 65 to 88 years, GH administered subcutaneously at an initial dose of 30 µg/kg, 3 times per week, then reduced to 20 µg/kg, was associated with carpal tunnel syndrome in 38% of women vs 7% of those taking placebo, and in 24% of men vs 0% taking placebo; edema in 39% of women (0% for placebo) and 30% of men (12% for placebo); and arthralgias in 46% of women (7% for placebo) and 41% of men (0% for placebo). Eighteen men treated with GH developed glucose intolerance or diabetes compared with 7 men in the nontreatment group.¹⁷

In a placebo-controlled clinical trial of GH (0.1 mg/kg/d of GH) for AIDS wasting syndrome in 510 patients, the most common reasons for dose reduction and/or drug discontinuation were arthralgia, myalgia, edema, carpal tunnel syndrome, and elevated glucose and triglyceride levels, with 36% of individuals reporting arthralgias (vs 11% of those taking placebo), 30% reporting myalgias (12% for placebo), and 26% reporting peripheral edema (3% for placebo).²¹ Because of these high rates of adverse effects,²² nonsustained improvements in quality of life^{23,24} and anabolic effects,^{24,25} and the drug's high cost, even the treatment of AIDS wasting syndrome with GH has little support.^{23,26,27} The doses used in these studies are similar to those suggested by antiaging Web sites selling GH.

Another concern is the possibility of an increased cancer risk with long-term GH treatment²⁸ and the potentiating effects of insulin-like growth factors (IGFs) on cancer.²⁹ Mukhina et al³⁰ reported that autocrine production of GH by mammary carcinoma cells facilitates cellular growth and suggested that such growth may be sufficient to cause breast carcinoma to become invasive and metastatic.

To our knowledge, no studies have assessed long-term efficacy or safety of GH administration as an antiaging intervention in humans. Proponents of GH claim that aging is caused by an age-related decline in GH levels and therefore GH supplementation can stop or reverse aging,^{3,14} but scientific findings counter or fail to support this hypoth-

esis. Transgenic mice that produce supraphysiological levels of GH for their age have markedly reduced life spans and experience premature onset of age-related cognitive changes.³¹ Rats with adult-onset GHD and decreased IGF-1 levels have a 30% decrease in tumor incidence and a 16% decrease in disease burden.³² Growth hormone-resistant and GH-deficient mutant mice experience substantially increased life spans.³³

Legal Distribution of GH in the United States

As is the case for anabolic steroids, the legal provision and distribution of GH is narrowly defined. In 1988 and again in 1990, Congress amended the Food, Drug, and Cosmetic Act (FDCA) to enact more stringent controls with higher penalties for offenses involving the distribution of anabolic steroids and HGH [codified at 21 USC §333(e)(1)].³⁴ In 1993, the provisions outlawing the distribution of specifically growth hormone were recodified as 21 USC §333(f) (pursuant to PL No. 103-80, §3(e), 107 Stat 775). Section 303 (f)(1) of the FDCA permits distribution of HGH in connection with (1) "treatment of a disease" or (2) "other recognized medical condition" that has been authorized by the Secretary of Health and Human Services.^{34,35} Provision of GH is legal for children with short stature (defined as a height >2 SDs below the mean for the child's age and sex) who have GHD, poor growth due to renal failure, Turner syndrome, or Prader-Willi syndrome, and for children small for gestational age (children who at birth were 2 SDs below the mean for weight or length or both who maintain a small body size beyond the age of 2 years)³⁶ and for idiopathic short stature³⁷ (defined as height >2.25 SDs below the mean for age and sex, or the shortest 1.2% of children).^{38,39}

In adults, the FDA has stated that distribution of GH is legal for only 2 conditions (S. Silverman, Director, Division New Drugs and Labeling Compliance, FDA, written communication, 2005 [may be viewed at <http://www.bumc.bu.edu/centenarian>]): wasting syndrome of AIDS (this does not include lipodystrophy²⁶) and GHD, the latter of which must meet 2 diagnostic criteria⁴⁰: biochemical diagnosis of adult GHD by means of a subnormal response to the standard growth hormone stimulation test (peak GH, <5.0 ng/L); and patients who have adult GHD either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or patients who were GH deficient during childhood.

The stimulation test for GHD is performed with GH-releasing hormone (or factor), arginine, glucagon, or insulin-induced hypoglycemia. Only 1 case per 10 000 adults per year meet these criteria for the diagnosis of GHD; 3 cases per 10 000 also include adults who received GH treatment as children.⁴¹ The prevalence of adult GHD in the United States is estimated to be 50 000, and the incidence is approximately 6000 per year, but a substantial portion of adults with GHD are not currently being treated with GH.⁴¹ Mea-

surement of IGF-1 levels (a proxy for GH levels) in older adults, when demonstrated to be lower than that of young adults, does not constitute a scientific^{39,42} or legally⁴⁰ accepted diagnosis of GHD.

Marketing and Distribution of GH for Antiaging

In the United States, GH is commonly marketed, distributed, and prescribed for antiaging under the pretext of “off-label use.”¹⁴ However, off-label distribution or marketing of GH to treat aging or aging-related conditions is illegal. Unlike most FDA-approved medications, GH can only be distributed for indications specifically authorized by the Secretary of Health and Human Services³⁵—aging and its related disorders are not among such indications.^{43,44} Furthermore, the FDA has clearly indicated that GH is not a dietary supplement.⁴³ Growth hormone was approved as a drug by the FDA in 1940⁴³ prior to enactment of the 1994 Dietary Supplements Health and Education Act and, because it is a drug, it cannot be classified as a dietary supplement.⁴³ In addition, dietary supplements must be intended for ingestion.⁴⁵ The FDCA defines the term “dietary supplement” in 21 USC 321 (ff)(2)(A)(i) to mean a product that is “intended for ingestion.” Consequently, a product that is not intended for ingestion cannot meet the definition of a dietary supplement.⁴⁴ Growth hormone is bioavailable only in injectible form, and therefore this is another reason why it cannot be classified as a dietary supplement.³⁹

The FDA’s position on the illegality of distributing GH as an antiaging treatment is conveyed in warning letters to Web sites marketing GH^{43,44} (other warning letters can be viewed at: <http://www.fda.gov/foi/warning.htm> and entering the term “growth hormone”). The penalties chapter of the FDCA states under section 303 [333]³⁵:

(f)(1) Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, or both.

(2) Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10 years imprisonment, such fines as are authorized by title 18, or both.

(3) Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act for the purposes of forfeiture under section 413 of such Act.

(4) As used in this subsection the term “human growth hormone” means somatrem, somatotropin, or an analogue of either of them.

(5) The Drug Enforcement Administration is authorized to investigate offenses punishable by this subsection.

The penalties for distribution or provision of GH for antiaging purposes are substantial. Per the FDA’s letter to Dr Perls: “Section 303 provides for up to five years in prison, or ten years if the offense involves a minor. It also permits

courts to impose fines of up to \$250 000 for an individual or \$500 000 for an organization, or alternatively, twice the gross gain or loss from the offense (see 18 USC § 3571), as well as forfeiture of property used in or derived from violations of the HGH law.” (S. Silverman, Director, Division New Drugs and Labeling Compliance, FDA, written communication, 2005 [may be viewed at <http://www.bumc.bu.edu/centenarian>]).

Those who distribute GH via the Internet violate another law. Per the FDCA, GH must be prescribed by a physician who, “based upon an individualized determination of a proper course of treatment, authorizes the drug’s distribution to a patient under his supervision”³⁴ (see also 21 USC § 353[b][1][B]).⁴⁶ Review of numerous Web sites that sell GH reveals either no steps taken to provide such supervision, or in the case of those who claim to provide supervision, the law may still be violated if the supervising physician never meets the patient (examples available on request). Distributing drugs such as anabolic steroids or GH in this manner is termed “misbranding,” a practice that in other contexts has resulted in the prosecution and conviction of laypersons, pharmacists, and physicians as a felony.³⁴

Common marketing practices regarding GH and related products may also be illegal. In a recent case brought before the US District Court by the Federal Trade Commission (FTC) regarding a defendant selling products claimed to contain GH,⁴⁷ the FTC stated several claims that illustrate findings that can lead to fines and disciplinary action:

1. “The dissemination of false advertisement for the purpose of inducing the purchase of a drug or device pursuant to 15 USC § 52(a) is an unfair or deceptive practice within the meaning of 15 USC § 45(a).”

2. “The defendant deceptively promotes and sells HGH products with claims that are wholly false and cannot be substantiated.”

3. “The defendant’s claims are false and cannot be substantiated with competent scientific evidence.”

Searching the Internet, numerous law-related Web sites, and specifically the FDA and US Department of Justice Web sites, reveals examples of lawsuits pertaining to distribution of GH for “antiaging.” Misleading claims led one company to voluntarily destroy \$515 000 worth of its HGH product.⁴⁸ Another company pleaded guilty to the felony charge of illegally distributing GH without physicians’ orders, paid a \$500 000 criminal fine, and forfeited \$1.25 million in profits made in sales of approximately 100 000 bottles of its GH oral spray.⁴⁹ Two Oregon physicians were prosecuted by the Oregon attorney general, with the assistance of the FDA and the US Department of Justice, for misrepresenting GH to consumers “as a harmless panacea for the effects of aging” while prescribing, promoting, and selling GH at their clinic and via the Internet.^{50,51} Two Florida businesses, named in an FTC complaint along with 2 individuals involved in the businesses, including one who is a physician, “agreed to a federal court order requiring them to pay up to \$20 million in

consumer redress—the largest monetary judgment ever obtained in an FTC health fraud case—to settle charges that they deceptively claimed that their pills and sprays would increase consumers' human growth hormone (HGH) levels and provide anti-aging benefits.⁵² The FTC indicated that the total sales of their products, including the dietary supplement “ultimate HGH” and the sublingual sprays “Master HGH” and “Super HGH” exceeded \$70 million. Importation and distribution of counterfeit GH has also been prosecuted.⁵³⁻⁵⁵

Responsibilities Regarding GH

Physicians and other health care professionals should be aware that current law explicitly prohibits the distribution of GH except for clearly and narrowly defined indications. Distribution for other uses, or off-label use, such as for anti-aging, age-related conditions, and enhancing athletic performance, are illegal.^{2,35,43,45} Although GH is not a schedule III drug, section 303 [333] f(5) of the FDCA clearly provides the Drug Enforcement Administration with the responsibility of enforcing the laws governing human GH.³⁵

Given the clinical concerns and the legal issues involved, we believe that physicians or other persons who currently market, distribute, or administer GH to their patients for any reason other than the well-defined approved (ie, legal) uses of the drug, should not do so. Pharmaceutical companies that manufacture GH should play a more effective role in making physicians and the public aware of the circumstances in which the marketing and distribution of GH are legal and illegal. Federal and state agencies should be allocated resources to better deal with the illegal distribution of GH. Finally, the FDA and professional and lay organizations are in excellent positions to conduct awareness campaigns to educate physicians and the public about the legal and medical ramifications of GH use for anti-aging.

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