HHS Public Access

Author manuscript

Sex Med Rev. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Sex Med Rev. 2018 January ; 6(1): 45–53. doi:10.1016/j.sxmr.2017.02.004.

The Safety and Efficacy of Growth Hormone Secretagogues

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Abstract

Introduction—Growth hormone (GH) increases lean body mass, reduces fat mass, increases exercise tolerance and maximum oxygen uptake, enhances muscle strength, and improves linear growth. Long-term studies of GH administration offer conflicting results regarding its safety, which has led to strict FDA criteria for GH use. The potential drawbacks of exogenous GH use are thought to be due in part to impaired regulatory feedback.

Aim—To review the literature on GH secretagogues (GHSs), which include GH releasing peptides (GHRPs) and the orally available small molecule drug Ibutamoren mesylate.

Method—Review of clinical studies on safety and efficacy of GHSs in human subjects.

Main Outcome Measure—Report on the physiologic changes due to GHS use in human subjects including its safety profile.

Results—GHSs' promote pulsatile release of GH that is subject to negative feedback, and may prevent supratherapeutic levels of GH and their sequelae. To date, few long-term, rigorously controlled studies have examined the efficacy and safety of GHSs, although GHSs may improve growth velocity in children, stimulate appetite, improve lean mass in wasting states and in obese individuals, reduce bone turnover, increase fat-free mass, and improve sleep. Available studies indicate that GHSs are well tolerated, with some concern for increases in blood glucose due to decreases in insulin sensitivity.

Conclusion—Further work is needed to better understand the long-term impact of GHSs on human anatomy and physiology, and more specifically in the context of a diversity of clinical scenarios. Furthermore, the safety of these compounds with long-term use, including evaluation of cancer incidence and mortality, is also needed.

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Conflict of Interest Statement

The authors report no conflicts of interest.

Keywords

Growth hormone; growth hormone secretagogue; growth hormone releasing peptide; hexarelin; ibutamoren; GHRP-2; GHRP-6

INTRODUCTION

Growth hormone (GH), which is produced by somatotroph cells of the anterior pituitary, exhibits pulsatile secretion that promotes linear growth in children by acting on the epiphyseal plates of the long bones(1). GH also increases lipolysis, stimulates protein synthesis, and antagonizes insulin action(1). While GH receptors exist in many organs and are responsible for some direct effects, many peripheral effects of GH are attributed to insulin-like growth factor 1 (IGF-1) (1, 2). IGF-1 is regulated via GH binding to a receptor homodimer, located primarily in the liver, which regulates intracellular signaling via a phosphorylation cascade involving the JAK/STAT pathway(1). Serum IGF-1 levels are a surrogate for GH levels because of IGF-1's relationship as both a downstream effector and upstream regulator of GH, as well as a half-life that is markedly longer than that of GH(1).

Due to its anabolic effects, the use of recombinant GH has been studied in GH deficient adults examining a variety of endpoints, including bone mineral density, exercise tolerance and performance, muscle strength, skin effects, immune function, and quality of life, among others(3). From these studies, we have learned that exogenous GH can increase lean body mass while reducing fat mass(4–6), increase exercise tolerance(7, 8), increase maximum oxygen uptake in adults(9–11), and enhance muscle strength and cross-sectional area(12).

Despite these benefits, GH use is restricted by the FDA to a discrete set of conditions(13, 14). Current indications for GH therapy in adults include 1) documented GH deficiency in childhood, 2) documented hypopituitarism as a result of pituitary or hypothalamic disease, surgery, radiation therapy, trauma or aneurysmal subarachnoid hemorrhage, 3) AIDS wasting syndrome(15–17), and 4) short bowel syndrome. Use of GH for anabolic applications, except in the setting of AIDS where GH has shown efficacy in alleviating lipodystrophy(15), improving muscle performance(16), and treating HIV induced muscle wasting(17) is not currently approved due to safety concerns(13). These concerns arose from large European studies that followed children on long-term recombinant GH therapy and observed increased mortality in the cohort(18). Other studies have linked exogenous GH use and increases in IGF-1 levels with an increased risk of malignancy(19). Carel et al. observed higher mortality rates from bone cancers and cerebral hemorrhage in patients on GH(18). However, GH supplementation did not correlate with mortality in a dose dependent manner, with no increase in mortality as a function of GH treatment duration or overall exposure. In contrast, a study using Denmark's nationwide population registry observed lower mortality in children receiving recombinant GH in comparison with age matched controls(20). More generally, complications arising from exogenous GH therapy may result from supratherapeutic levels of GH and the bypass of regulatory feedback mechanisms(19, 21).

Given the potential risks of exogenous GH use, alternative therapies that avoid these risks would be welcome additions in the management of GH-deficient patients. Growth hormone

secretagogues (GHSs), which include growth hormone releasing peptides (GHRPs) and small molecule drugs that can stimulate secretion of endogenous GH, may provide the benefits of GH while minimizing negative sequelae. In this review, we summarize the literature examining the safety and efficacy of GHSs.

History and Physiology of Growth Hormone Secretagogues

GHRPs were first synthesized in Cyril Bowers' laboratory in 1977 as a series of synthetic enkephalin opiate analogues that stimulated GH release from rat pituitary cells *in vitro*(22) (Table 1). The first peptide that was found to stimulate GH release from rat pituitary cells was Tyr-DTrp^2-Gly-Phe-MetNH_2. This original GHRP mimics growth hormone releasing hormone (GHRH), but was found to only weakly stimulate GH secretion *in vitro*(23). The first GHRP with significant *in vivo* activity was a hexapeptide, His-DTrp-Ala-Trp-DPhe-LysNH_2, also known as GHRP-6.(24, 25) Despite mimicking natural GHRH action, GHRPs do not bind the seven-transmembrane domain, G protein-coupled GHRH receptor (GHRH-R), which functions via the protein kinase A pathway. Rather, GHSs bind a receptor (GHS-R) that is coupled via members of the Gq/i family of proteins and that activates phospholipase C(24, 26). Subsequent work showed that GHRPs did not attenuate GHRH action when used prior to GHRH injection, but that GHRH and GHRP, when used together, synergistically stimulated GH release(24, 27). Subsequent work found that GHRPs act on both the pituitary and the hypothalamus, and that these peptides stimulate the release of GH without affecting the normal negative feedback mechanisms in the GH pathway that include somatostatin and IGF-1(24) (27).

Broad clinical use of GHRPs is limited in part due to the need for frequent dosing and injectable route of administration, given their poor oral bioavailability and short half-lives(27). For example, GHRP-6's oral bioavailability is 0.3% and half-life is 20 min(28). To identify a small molecule drug with oral bioavailability and high potency, Merck screened non-peptide compounds for GHS activity in a rat pituitary cell assay using GHRP-6 as a template. From directed screening of approximately 100 compounds, a substituted racemic benzolactam was identified that increased GH secretion from rat pituitary cells. Through chemical modification to increase potency, L-692,429 was created as a small molecule peptidomimetic agonist for GHRP-6 receptors. Although the oral bioavailability of L-692,429 and serum half-life were superior to those of GHRP-6, the overall pharmacokinetic properties were not sufficient for once daily oral administration. Continued work and modification of this structure led to compound L-163,191 which was highly orally bioavailable and specific to the GHS-R(27). No adverse effects of L-163,191 were observed during this 14 day study, and the drug entered clinical development as MK-0677, also known as ibutamoren mesylate.

Ibutamoren and the GHRPs discussed in this review are not currently FDA approved. However, several of these are available by prescription through compounding pharmacies both in the United States and abroad. Private entities have marketed ibutamoren and GHRPs as supplements, and the drugs are also available through internet sites that focus on supplementation. Of note, sermorelin and tesamorelin are GHRPs with similar mechanisms of action as ibutamoren and the other GHRPs discussed in this review. Sermorelin and

tesamorelin mimic GHRH and act as GHRH-R agonists, acting synergistically with ibutamoren. Similarly to the GHRPs, GHRH analogs are not FDA approved, but are available by prescription through compounding pharmacies and internet vendors.

Human Studies

Much of the work involving GHS administration in humans has examined serum GH or IGF-1 secretion after short treatment courses, finding that GH and IGF-1 levels increase in both adults and children after GHS administration(29–38). However, few studies examining clinically significant endpoints such as body composition, exercise tolerance, and quality of life are currently available, limiting the ability to evaluate the clinical utility of GHS's.

Use of Growth Hormone Secretagogues in Children with Short Stature—As a potential replacement for recombinant GH, one of the most robust and long term studies using GHRPs was performed by Laron et al., who studied 8 short prepubertal children (7 boys, 1 girl) given 60 mcg/kg hexarelin, a GHRP that is structurally similar to GHRP-6, three times daily via an intranasal route for up to 8 months. Hexarelin stimulated IGF-I secretion, with serum levels rising from 10.4±3.9 to 14.1± 4.6 nmol/l ($P < 0.004$). An increase in linear growth velocity, from 5.3±0.8 to 8.3±1.7 cm/year ($P < 0.004$), was also observed, and subjects gained weight, though BMI and body composition were not assessed(39). A subsequent study examined the effects of GHRP-2 in 10 prepubertal children with growth deficiency, showing that while GHRP-2 appears to have a transient stimulatory effect on appetite, it does not lead to a durable increase in BMI(40). GHRP-2 also increased growth velocity in a group of 6 prepubertal GH-deficient children treated with GHRP-2 for continuous successive 2-month periods, with daily bedtime injections in doses of 0.3, 1.0, and 3.0 mcg/kg for each of the 2 month blocks, respectively. During the 6 months of increasing GHRP-2 dose, growth velocity increased when compared with the 6 months prior (5.3±0.8 vs. 3.0±0.5 cm/year, $P < 0.05$), or during the 6 months following discontinuation of treatment (3.3±0.4 cm/year)(41). A third study evaluating GHRP-2 in doses of 5–15 mcg/kg two or three times per day in 15 children with short stature further confirmed the previously observed increases in growth velocity following treatment. Six of 15 patients remained on treatment for 18–24 months and continued to see an average increased growth velocity of 6.0±0.4 cm/year(42). Ibutamoren mesylate has also been used in the setting of GH deficient children, but not as extensively as the GHRPs, with a single study demonstrating increases in GH and IGF-1 levels after only 7 days of therapy, without examining growth rates(43).

Use of Growth Hormone Secretagogues in Wasting States and Recovery—Laferrere et al. observed increases in appetite during GHRP-2 administration. Their first study, a randomized, double-blind examination of subcutaneous GHRP-2 or saline in 7 lean healthy males followed by measurement of food intake during a buffet-style meal found that males receiving GHRP-2 ate 35.9±10.9 % more than placebo, with every subject on GHRP-2 increasing their food intake even when this was calculated per kilogram of body weight (136.0±13.0 kJ/kg vs. 101.3±10.5 kJ/kg, $p=0.008$)(44). A second study was similarly designed, with 10 lean and 9 obese subjects treated using both a high dose (1 mcg/kg/hr) and a low dose (0.1 mcg/kg/hr) of GHRP-2, as well as a placebo. GHRP-2 infusion significantly

increased ad libitum food intake in a dose-dependent manner by 10.2±3.9 % at low dose (P = 0.011) and by 33.5±5.8 % at high dose (P = 0.000) when compared to placebo. Obesity status did not influence the effect of GHRP-2 on food intake(45). Both studies showed increased appetite scores at baseline when 1 mcg/kg/hr of GHRP-2 was administered when compared with placebo(44, 45). The increased appetite associated with GHRP-2 was capitalized on in a Japanese case report of a woman with a 20-year history of anorexia nervosa that was treated with GHRP-2. Over 14 months, she increased her food intake, noting decreased early satiety and improvements in hypoglycemic symptoms. These subjective measures resulted in a 6.7 kg increase in body weight during treatment(46).

Van den Berghe et al. proposed that GHRPs may be useful in combating catabolism in chronic illness. In 33 men with baseline chronic illness including cardiovascular, pulmonary, or abdominal surgery or polytrauma compared to 50 age-matched controls, men with chronic illness had suppressed pulsatile GH and luteinizing hormone (LH) secretion and low serum levels of IGF-I, IGFBP-3 and acid-labile subunit (ALS) (P < 0.0001 each), as well as thyroid stimulating hormone (TSH), T3, and T4 (P < 0.0001) and total and free testosterone (P < 0.0001) levels. In the 9 men with chronic illness in the GHRP-2 treatment group, an infusion of 1 mcg/kg/h for 5 consecutive days resulted in resumption of GH secretion and normalization of IGF-I, IGFBP-3 and ALS levels(47). These results suggest that while GHRPs may stimulate GH release in a catabolic state, reversing a hypercatabolic state may be most effectively accomplished via normalization of all deficient hormones. Ibutamoren mesylate was used by Murphy et al. in 1998 to slow nitrogen wasting in a catabolic state. In this study, 8 healthy young volunteers were calorically restricted for 14 days, and for the last 7 days were given ibutamoren or placebo. After a 14–21 day washout period, the other treatment (placebo for the ibutamoren group and ibutamoren for placebo group) was given during the second week of the second 14 day period of caloric restriction. During the second week of the study, mean daily nitrogen balance was 0.31±0.21 g/day in the ibutamoren group compared with −1.48±0.21 g/day in the placebo group (P< 0.01), demonstrating preservation of nitrogen balance in the setting of ibutamoren(48).

Bone turnover in the elderly may also be improved by ibutamoren, with 9 weeks of ibutamoren treatment showing a 29.4% increase in mean serum osteocalcin, a 10.4% increase in bone-specific alkaline phosphatase (P < 0.001) and a 22.6% increase in urinary N-telopeptide crosslink excretion (P < 0.05) when compared with placebo(49). Subsequent work examined the role of ibutamoren in facilitating recovery of elderly patients from hip fracture. A double-blind, placebo controlled study that included 161 hip fracture patients examined the impact of ibutamoren vs. placebo on functional improvements during rehabilitation(50). More significant increases in IGF-1 levels were observed in the ibutamoren group when compared with placebo (84% vs. 17%, respectively). When assessing functional outcomes, the ibutamoren group did not evidence a significant impact in quality of life, although 3 out of 4 lower extremity performance measures improved in this group. There was also a trend towards more independent living in the ibutamoren group in all patients, and in particular in 70% of those who were independent prior to hip fracture (P=0.036)(50). A second, smaller study (n=123) with a similar design evaluating ibutamoren compared with placebo in hip fracture recovery observed improved stair climbing power and gait speed in the ibutamoren group. However, these increases were so small that they were

not considered meaningful improvement(51). Though the above work suggests a positive impact of GHSs on anabolism, additional study is needed to determine whether the slowing of catabolism by GHSs affects mortality, hospital length of stay, or results in functional improvements by reducing protein breakdown and increasing anabolism.

Growth Hormone Secretagogues and Body Composition—Normalization of GH release and the resulting increase in lean mass and reduction in fat mass may most significantly benefit obese individuals. Cordido et al. showed that GHRP-6 can increase GH secretion in 19 obese subjects(52). However, in a follow-up study, the responses of 12 obese and 8 non-obese subjects to a combination of GHRH and GHRP-6 (100mcg each, intravenously), were compared, with a lower GH response observed in obese than in non-obese patients(53). While obesity can impair GH secretion(54), these results demonstrated that the combination of GHRP and GHRH can help restore some GH secretion. A later study examined the GH response to GHRP-6 and GHRH observed a blunted response to the co-administration of GHRP-6 and GHRH in obese, non-insulin dependent diabetics (n=13) when compared with healthy controls (n=8)(55). These results demonstrate that obesity blunts but does not eliminate the effect of GHRP on GH secretion, and that the synergistic effect of combination therapy with GHRH may be useful in restoring the GH axis in obese individuals. These studies, however, are limited by one-time administration of drug and a lack of somatic endpoints that assess changes in body composition over time.

Ibutamoren has been used in healthy obese men for longer periods than GHRPs. A two-month randomized, double-blind, parallel, placebo-controlled trial with 24 men showed a 3kg increase in fat free mass (FFM) in the ibutamoren group when compared with placebo ($P < 0.01$)(56). This trial did not show changes in visceral or abdominal fat mass when these parameters were examined(56). Recently, a study of 25 women and 21 men with Prader-Willi syndrome examined the impact of long-term exogenous GH vs. placebo on body composition in these patients. Significant fat losses were observed, with visceral fat decreasing by an average 22.9 ml ($P = 0.004$), abdominal subcutaneous fat by 70.9 ml ($P = 0.003$) and thigh fat by 21.3 ml ($P = 0.013$). These fat losses occurred in conjunction with increases in thigh muscle (6.0 ml, $P = 0.005$) and lean body mass (2.25 kg, $P = 0.005$), with a decrease in total fat mass of 4.20 kg ($P < 0.001$). After one year, open label treatment for an additional 2 years demonstrated that the positive effects on body composition were maintained(57).

Changes in body composition mediated by enhancement of GH signaling can also benefit the elderly. Nass and colleagues, in a two-year, double-blind, randomized, placebo-controlled, modified-crossover clinical trial of 65 healthy elderly patients, found that daily ibutamoren increased GH and IGF-I levels to those of healthy young adults without serious adverse effects. Fat free mass increased 1.1 (95% CI 0.7–1.5) kg in the ibutamoren group, in contrast with a decrease of −0.5 (−1.1−0.2) kg in the controls ($P < 0.001$)(58). Furthermore, low density lipoprotein cholesterol decreased −5.4 (−10.4 – −0.4) mg/dL in the Ibutamoren group ($P = 0.026$), with no differences in total or high density lipoprotein cholesterol observed. In this trial, increased FFM did not result in increased strength, and abdominal visceral fat content was not affected(58).

Growth Hormone Secretagogues and Sleep—Work examining the effects of GHRPs on sleep derives primarily from a series of studies by Frieboes et al. The group's 1995 study examining 7 healthy young males showed that repeated intravenous boluses of GHRP-6 given during sleep increased serum GH, ACTH and cortisol levels, as well as mean time spent in stage 2 sleep without altering slow wave sleep patterns(59). Several additional studies examined how dosage and route of administration affected sleep patterns, and compared the sleep-endocrine effects of GHRPs in 7 subjects given 300 mg/kg GHRP-6 orally, in 7 subjects given 30 mg/kg GHRP-6 intranasally, and in 9 subjects given 30 mg/kg GHRP-6 sublingually. No significant changes in sleep patterns were observed for any non-intravenous GHRP-6 formulations(60). A final study by these authors examined sleep in 7 healthy males treated with hexarelin and placebo either 1 week before or after hexarelin administration. Similar to the first study, the authors observed increases in GH and prolactin levels throughout the night, and in ACTH and cortisol levels during the first half of the night. Shorter duration stage 4 sleep was observed during the first half of the night in patients on hexarelin, with a non-significant trend towards longer stage 2 sleep during the second half of the night in patients on hexarelin(61).

Ibutamoren has even more profound effects on sleep when compared with the GHRPs. In one crossover study of 8 young male subjects 18–30 years old and six older male subjects 65–71 years old treated with 25mg ibutamoren daily, a 50% increase in stage 4 sleep duration and a >20% increase in REM sleep duration were observed in the young cohort when compared with placebo ($P<0.05$). In older adults, a 50% increase in REM sleep ($P<0.05$) and a decrease in REM latency ($P<0.02$) were observed(62). Both groups showed decreases in deviation from normal sleep duration as well ($P<0.03$ for each group)(62).

Safety of Growth Hormone Secretagogues

Within the limits of current literature, growth hormone secretagogues appear safe, with few of the studies cited in this review observing serious adverse events (AEs) with the use of GHRPs. However, safety data are limited due to the overall short durations and small sizes of most studies. Longer term studies with ibutamoren are available, and of these, only one observed significant AEs related to ibutamoren use. Adunsky et al. examined the role of ibutamoren in recovery from hip fracture in 123 elderly patients during 24 weeks of treatment, and was the only randomized double-blind placebo-controlled trial that was stopped early due to concerns that ibutamoren may increase the rate of congestive heart failure (CHF)(51). Four patients in the ibutamoren group (6.5%) and one in placebo group (1.7%) developed CHF during the study, though the higher CHF rate in the ibutamoren group may have been due in part to higher baseline blood pressures in that group(51). More generally, more AEs were reported in patients on ibutamoren than in those on placebo (48 (77%) vs. 33 (55%), respectively) in this study. These findings contrast with a similar randomized, double-blind, placebo controlled trial by Bach et al. that also examined the use of ibutamoren for 6 months in 161 elderly patients recovering from hip fracture. In this study, serious AEs were similarly distributed between the ibutamoren and placebo groups, apart from more thromboses reported in the ibutamoren group, though these were not thought to be drug related(50). However, more patients discontinued treatment due to a clinical AE in the ibutamoren group than in the placebo group ($P < 0.05$). While the above

studies observed numerous AEs, another randomized, double-blind, placebo-controlled trial evaluating the effects of 4 weeks of ibutamoren administration in 32 healthy elderly patients observed no AEs(63).

In three, 2–9 week randomized, double-blind, placebo-controlled clinical studies examining the effects of ibutamoren on serum IGF-1 levels and markers of bone turnover in 187 elderly adults, treatment was well tolerated, with no serious drug-related AEs observed in patients on ibutamoren. Across the three trials, only two subjects on ibutamoren discontinued treatment due to a drug-related AE(49). A longer, 18-month study of 292 postmenopausal women allocated into placebo, ibutamoren, alendronate, and combination alendronate/ibutamoren treatment groups showed that ibutamoren was well tolerated, as only 3/36 patients in the placebo group, 6/36 in the ibutamoren only group, and 11/111 in the ibutamoren and alendronate group dropped out of the study due to clinical or laboratory AEs related to study treatment(64). One of the longest studies reporting on GHS use was a randomized double-blind placebo-controlled 2-year crossover study of ibutamoren and placebo in 65 healthy elderly participants by Nass et al. The only AE that occurred more often in the treatment group was increased appetite, which was reported in 29/43 (67%) subjects on ibutamoren and 8/22 (36%) subjects on placebo (P = 0.02)(58). Another double-blind, multicenter study of 563 patients with mild to moderate Alzheimer's disease were randomized to receive ibutamoren or placebo daily for 12 months, with serious drug-related clinical AE rates that were comparable between groups. Adverse events that led to discontinuation of study therapy, but not dropout from the trial, occurred in 32 (11.3%) patients on ibutamoren and in 29 (10.4%) on placebo ($P = 0.787$). Fewer patient deaths were observed in the ibutamoren group and none were attributed to ibutamoren(65). Although no studies longer than 2 months have been performed in obese individuals, 2 months of daily 25 mg ibutamoren treatment in 12 obese individuals was well tolerated compared to 12 obese controls(56).

Blood glucose control and hyperglycemia have also been examined in the setting of GHS use. Elevations in IGF-1 levels in patients on GHS's lead to increased insulin insensitivity, which can result in blood glucose elevations. Nass et al., in their 2-year modified crossover trial in 65 healthy elderly patients found that fasting blood glucose increased with ibutamoren but not with placebo. Mean HbA1c increased with ibutamoren and decreased with placebo(58). Adunsky et al. reported four patients on ibutamoren (6.5%) with elevated blood glucose, compared with one patient on placebo (1.7%). Three patients on ibutamoren had increased HbA1c (4.8%) levels compared with none on placebo(51). The trial by Bach et al. observed significant increases in serum glucose and HbA1c in the ibutamoren group as well(50). In 32 healthy elderly patients, Chapman et al. observed that 25 mg of daily ibutamoren increased glucose concentrations by 25.3% and 26.9% above baseline at 2 and 4 weeks, respectively. A large trial in Alzheimer's patients found a more patients with increased blood glucose levels in the ibutamoren group (15.4%) than the placebo group (4.6%), with similar differences in HbA1c levels between the groups(65). In a 2-month trial of ibutamoren in 24 obese males, fasting glucose and insulin levels were unchanged, whereas an oral glucose tolerance test showed impairment of glucose homeostasis at 2 and 8 weeks(56). Hyperglycemia resulting from ibutamoren use has been observed in other studies

as well(48, 49, 64). Of note, no safety data examining malignancy and mortality rates are currently available for GHS's.

CONCLUSIONS

Relatively few studies examining the effects of GHS's are currently available, though existing studies support beneficial roles for these drugs in raising GH levels and impacting patient outcomes. Few studies evaluating large cohorts for sustained durations of GHS treatments are currently available, limiting the ability to rigorously compare the effects of GHS's with those of GH. Available data support increases in GH and IGF-1 levels with GHS treatment, but provide few objective insights on the effects of these drugs on body composition or other important endpoints. Although available studies support a beneficial effect of GHS's on growth velocity in children, appetite stimulation, positive effects in wasting states and in obese individuals, bone turnover, FFM, and sleep, parameters that remain to be investigated include hospital recovery time, functional muscle parameters or adiposity changes in the context of an exercise program, and long-term large safety data. The current literature supports an increased risk for hyperglycemia in the context of GHS use, with few other AEs that are directly attributable to GHS use. However, larger safety studies are needed to accurately compare the safety of GHSs with that of exogenous GH. Future work should also focus on determining the effects of GHSs on patient outcomes in a variety of conditions, as well as on body composition in the setting of exercise and recovery from catabolic states.

Based on the literature, current indications for the use of GHS's include treatment of wasting and as treatment for GH deficiency. We recommend a starting dose of 0.1 mg of the GHRPs, which is well tolerated and efficacious in raising IGF-1 levels. Most GHRPs require three times daily dosing given their lack of oral bioavailability and short half-life. This dosing frequency helps to mimic GH peaks that occur throughout the day in normal healthy adults. A starting dose of 25 mg by mouth daily for ibutamoren is recommended given that this is the dose studied in randomized controlled trials. We recommend following these patients with regular examinations for changes in body composition and IGF-1 levels during GHS treatment, as well as with blood glucose and Hb A1c monitoring.

Acknowledgments

AWP is a K12 scholar supported by a Male Reproductive Health Research (MRHR) Career Development Physician-Scientist Award (Grant # HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program

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Table 1

Characteristics of Growth Hormone Secretagogues

Name	Oral Availability	Half-Life	Benefits	Side Effects
DTrp2(25)	No *in vivo* data; *in vitro* data only	No *in vivo* data; *in vitro* data only	No *in vivo* activity	No *in vivo* activity
GHRP-6(66)	0.30%	0.30 hr	Restoration of GH secretion in the obese(52, 53), increased time in stage 2 sleep(59)	Transient increase in cortisol (59)
GHRP-2(66, 67)	0.30–1.0%	0.52 hr	Increase in growth velocity in children(41, 42) Increase in appetite (44, 45) Weight gain in anorexia (46) Normalization of IGF-1 in critical illness(47)	Transient increase in appetite(40), Transient increase in cortisol (45)
Hexarelin(66, 68)	0.20%	0.83 hr	Increased growth velocity in children(39)	Shorter stage 4 sleep in first half of night(61)
MK-0751 (L-692,429)(27, 66, 69)	Negligible	4.7 hr	Increased GH secretion(37, 38)	Flushing and warm sensation(37, 38) Transient increase in cortisol and prolactin(38)
Ibutamoren (MK-0677, L-163,191) (27, 69)	>60%	4.7 hr	Reversal of nitrogen wasting(48) Functional lower extremity improvement post hip fracture(50, 51) Increase in FFM (56, 58) Decreased LDL(58) Longer REM sleep and shorter sleep latency(62)	Transient increase in cortisol and prolactin(48, 56) Musculoskelectal pain and fluid retention(49, 50, 58) Increase in insulin insensitivity(50, 51, 56, 58, 65), Transient increase in appetite(58)