A New Era in Relieving the Burden and Improving Health Outcomes of Children with Growth Hormone Deficiency

OVERVIEW

Growth hormone deficiency (GHD) specialists Sara DiVall, MD, and Kevin Yuen, MD, explore ways to optimize outcomes in the diagnosis and treatment of GHD in children, including considerations for the use of long-acting growth hormone (LAGH) products. Topics include the epidemiology, clinical manifestations, and burden of GHD in children and adolescents, evidence-based diagnosis of GHD, guidelines and recommendations for treatment, integrating shared decision-making with patients and/or their parents to develop and modify the treatment plan, and clinical trial data regarding daily and new and emerging LAGH products. Case studies based on common clinical scenarios are discussed to examine how to apply this information in clinical practice to optimize long-term self-management.

CONTENT AREAS

Epidemiology
Burden of GHD
Diagnosis
Shared Decision-Making
Somatropin Products
New/Emerging Long-acting Growth Hormone Products
Optimizing Outcomes

FACULTY

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TARGET AUDIENCE

This activity was developed for pediatric endocrinologists, pediatricians, nurse practitioners, physician assistants and other healthcare providers who treat children and adolescents with growth and growth hormone disorders.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Implement key treatment recommendations for children and adolescents with growth hormone deficiency
- Implement shared decision-making to help children and adolescents and their parents select a growth hormone product based on patient characteristics and needs and product labeling
- Initiate, titrate, and monitor growth hormone therapy in children and adolescents based on patient response and tolerability
- Describe the safety and efficacy of emerging long-acting recombinant human growth hormone therapies and their potential use in children and adolescents

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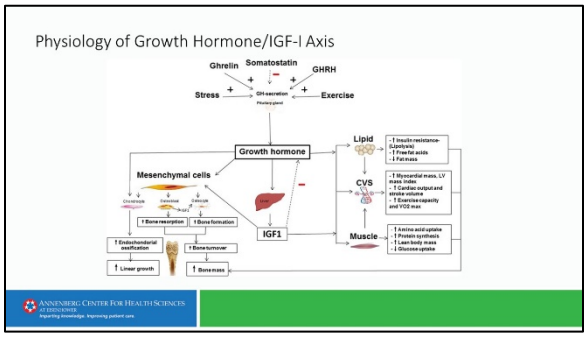
Editor's Note: This is a transcript of a webcast presented in February 2022. It has been edited and condensed for clarity.

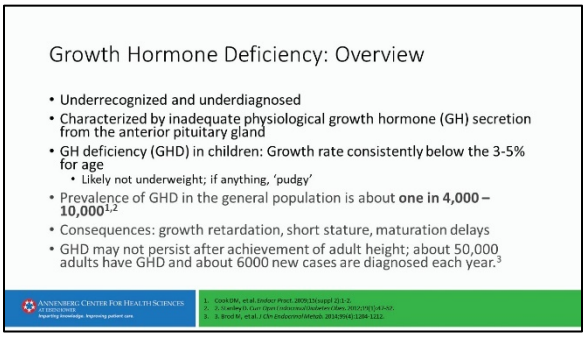
EPIDEMIOLOGY

PHYSIOLOGY AND ETIOLOGY OF GHD

Growth hormone is primarily produced in the pituitary gland, in the anterior lobe of the pituitary gland and is regulated by many factors. Stress plays an important role on growth hormone-releasing hormone or GHRH, somatostatin, ghrelin and exercise.



These hormones modulate and act on secreting the growth hormone in a timely manner and in a manner where growth hormone is expected to be secreted in a specific time of the day. When growth hormone is produced, it then acts on many organs. It acts on the liver to generate IGF1, which is stimulating insulin-like growth factor, which is primarily secreted from the liver, under the control of growth hormone, and acts on many organs including the bones, muscles, the lipids, and cardiovascular system. It acts on the bones to cause bone resorption and bone formation. It also promotes linear growth. It increases the changes in the lipids, particularly free fatty acids, and reduces fat mass. It also has particular effects on the cardiovascular system, particularly the heart and the pumping action of the heart, and also the muscles, particularly in terms of increased protein synthesis and a reduction in glucose uptake.



In terms of growth hormone deficiency, what exactly is this condition? It is a condition that is often underrecognized and therefore underdiagnosed. It is often characterized by physiological growth hormone secretion from the anterior pituitary gland where there is insufficient production of this hormone. It occurs both in children and also in adults. Particularly in children, you can see that when growth hormone deficiency occurs, the growth rate consistently falls below the 3% to 5% for the particular age. The prevalence for growth hormone deficiency in the general population is estimated to be approximately 1 in 4,000 to 10,000 and, for children, growth retardation and short stature is usually the main manifestation of how these patients present for medical attention.

If growth hormone deficiency in childhood persists in adulthood, you can have persistent growth hormone deficiency that occurs as the patient goes through into adulthood. But often, growth hormone deficiency may not persist after achievement of adult height and about 50,000 of adults with growth hormone deficiency, and

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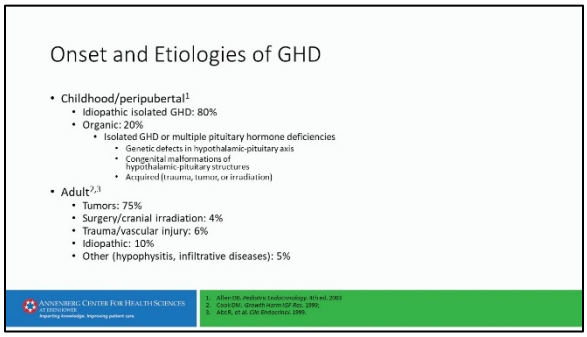
about 6,000 new cases of adult growth hormone deficiency, are diagnosed each year. That's taking into consideration childhood-onset growth hormone deficient patients transitioning into adulthood.

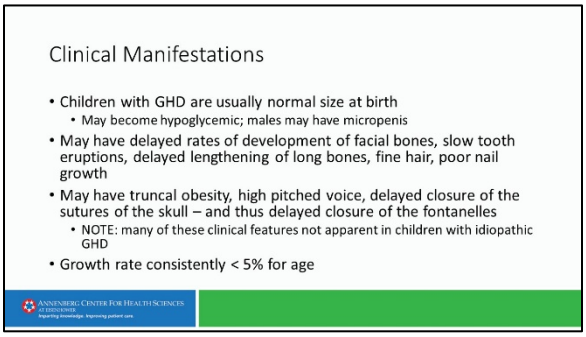


What actually causes growth hormone deficiency? In childhood or peripubertal stage, idiopathic, meaning often the cause is unknown, makes up about 80%, so primarily this is the main cause of growth hormone deficiency. The majority of it is idiopathic and isolated growth hormone deficiency, and 20% is made up of organic causes which could be related to genetic defects in the hypothalamic-pituitary axis, congenital defects and also acquired defects, such as tumors in the hypothalamic-pituitary region, head injury or surgery or radiation to tumors that induces this condition.

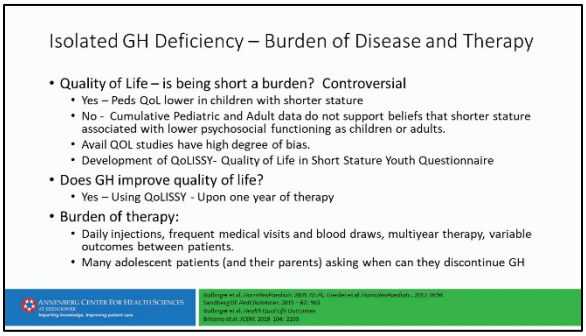
In adults, tumors make up the majority of the causes of growth hormone deficiency, 75%. And the treatment for such tumors, such as surgery and cranial irradiation, makes up 4%, trauma and vascular injury about 6%. And in 10%, the cause is idiopathic or unknown, and the remainder is made up of infiltrative diseases and inflammatory diseases, such as hypophysitis.

CLINICAL MANIFESTATIONS AND BURDEN OF DISEASE

The physical manifestations of growth hormone deficiency, whether congenital or acquired, are often nonspecific. Children with growth hormone deficiency are generally born appropriate for gestational age, not necessarily small for gestational age. Hypoglycemia or micropenis may be the only clue that you have to the diagnosis at birth.



Later on in childhood, children will have delayed bone maturation which may manifest as delayed tooth eruptions and lengthening of long bones. The other features, such as truncal obesity and high-pitched voice, are also very nonspecific signs of growth hormone deficiency. The most specific sign of growth hormone deficiency is linear growth. So, a growth rate that is consistently less than 5 percentile for age over a course of six to 12 months is the most specific time, sign for growth hormone deficiency.



Given that, given that 80% of diagnosed children have idiopathic isolated growth hormone

deficiency and the diagnosis of growth hormone deficiency can be open to interpretation. More on that in later slides. A question that needs to be asked: is the quality of life improved by growth hormone? Central to this question is the very first question: is quality of life itself lowered by being short? As with everything in medicine, you get a different answer depending on whom you ask and which study you look at. Some studies, which use the Peds Quality of Life measurement, showed that quality of life was lower in children with shorter stature. Other studies, using the same quality of life tool or other peds-specific quality of life tools, showed that there is no lower quality of life in children with shorter stature or adults with shorter stature, and that adults with shorter stature have typical psychosocial functioning.

These same critics also say that the available quality of life studies do have a high degree of bias in their reporting. So, this varying data and opinions, you know, prompted the field to develop the Quality of Life in Short Stature Youth Questionnaire. This is called the QoLISSY questionnaire. This was developed in the early 2010s to have a very specific tool to measure quality of life in kids with short stature. They've been used in a small number of studies, the QoLISSY has. There is a study that showed that, using this QoLISSY, that children with growth hormone deficiency were assessed before and after 1 year of growth hormone treatment and their quality of life was improved after that 1 year of growth hormone treatment. And we are awaiting further studies using this tool with a longer time on growth hormone, longer than 1 year, to see if this improvement in quality of life endures.

Of course, with the benefits of growth hormone on height which is well defined, and the possibility that growth hormone improves quality of life, one must balance these potential benefits of therapy with the burden of therapy. The burden of therapy includes the burden of having to do daily injections to achieve the height outcomes and frequent medical visits, at least twice, preferably 3 to 4 times yearly, to monitor therapy and side effects of therapy. And with blood draws for safety as well.

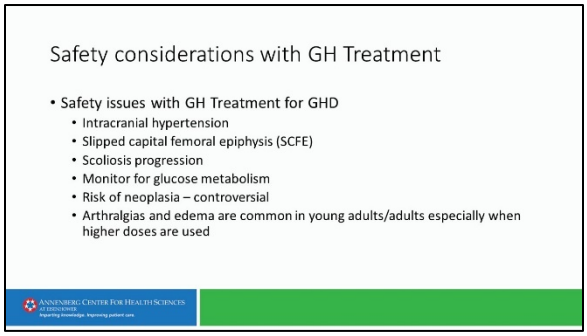
Growth hormone has a burden of therapy because it takes many years to achieve its outcomes and this many-year therapy can be difficult for the patient to endure while they're waiting for these height outcomes. And also, as a clinician, there can be variable outcomes between treated patients. So, guiding patients as far as how they're doing and how the growth hormone is working for them can be challenging because it varies very differently between patients.

And I know all these burdens can culminate in the adolescent patient, as it does for many other diseases. A common question that I have, and any practitioner who sees patients and guides patients on growth hormone therapy hears, is the adolescent and even their parents asking: when can I discontinue, is it still working for me, what are the benefits of continuing? I've been on this for many years! So, growth hormone therapy can have a significant burden on families and patients.

Safety of Daily GHD Treatments

The incidence of adverse effects of growth hormone are well defined because of growth hormone registries and post-marketing surveillance registries. Growth hormone was—recombinant growth hormone—was approved in 1985 and these registries were active until the early 2000s, and therefore these registries

contain thousands, up to 10s to 100s of thousands of children from whom we can collect the safety data.



These registries and surveillance has established that while children are on growth hormone it is very safe, less than 3% of children have any sort of side effects. The idiopathic intracranial hypertension occurs in every 1 in 1,000 or 1 in 2,000 children. Another parameter of occurrence is per 100,000 treatment years, and its incidence is 28 per 100,000 treatment years. The incidence of intracranial hypertension usually happens in the first 3 months of therapy and is dose-dependent, the higher the dose, it's more likely to occur. It also occurs more commonly in those with organic growth hormone deficiency.

Slipped capital femoral epiphysis occurs less often, anywhere between 1 in 5,000 to 1 in 10,000 children. It can occur later in therapy, years into therapy, and is associated with a rapid height gain. Growth hormone is also associated with scoliosis progression, not initiation, because it does increase linear growth, and because growth hormone lowers insulin sensitivity, it may induce or move people into diabetes in those at high risk for development of diabetes. The risk of primary neoplasia while on growth hormone is negligible to nothing. The risk of secondary neoplasia for people on growth hormone who already had their primary neoplasia is also not increased. Studies have shown that children who've had a primary cancer and subsequently treated with growth hormone and those treated with irradiation may develop meningiomas, not at a higher rate, but earlier than those not treated with growth hormone.

The long-term effects of growth hormone on risk of neoplasia, ie, decades after discontinuing therapy, is quite controversial. This assessment of this risk is primarily studied in Europe, at a European consortium of countries, and within this consortium, some countries have reported a higher-than-expected incidence of cerebrovascular events in the third decade of life. So, 2 to 3 decades after treatment. While other countries have not reported this higher-than-expected incidence. So, this information to tell our patients is controversial at this time. And, as young adults and adolescents approach growth plate fusion and they're approaching the end of growth hormone treatment for growth, arthralgias and edema can occur, especially when the higher doses are used in this age group.

DIAGNOSIS

Typical Growth Patterns

Since the most reliable clinical sign of growth hormone deficiency is a growth rate, we present here the values for the growth rate at the 50th percentile for each age. Note that during the school-aged years, between 4 and 10, the average growth velocity was 5 to 6 cm per year and the growth velocity of less than 5 percentile for age in this age group is equivalent to less than 4 cm per year. And this is the personal cut-off that I use that I recommend where evaluation for possible growth hormone deficiency or growth disorder occurs.

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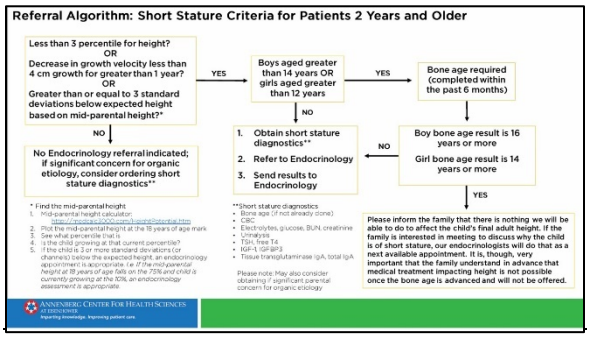
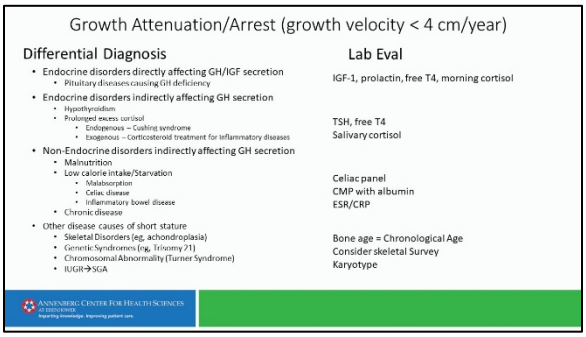
I list constitutional delay of growth and puberty here because children with con delay often have growth rates approaching that 4 cm per year or even less, especially between age 10 and age 14 when they should be starting puberty. It can be difficult to differentiate these children from children with a growth disorder, and I find that family history is key as con delay is an autosomal dominant phenomenon, and often there is a positive family history, in a parent, of delayed puberty.

Algorithm for Specialty Referral



Differential Diagnosis for GHD

The differential diagnosis of growth attenuation is very broad and I listed the differential diagnoses here under the subsections endocrine disorders directly or indirectly affecting growth hormone and IGF-1 secretion, non-endocrine disorders that may indirectly affect growth hormone secretion, chronic diseases or diseases primarily of the skeleton or caused by genetic syndrome.



In some cases, the physical exam and history can include or exclude these specific endocrine causes. In many other cases, they do not, and it's especially difficult if you have a normal healthy child who has a normal physical exam. In most cases, I and others end up using the laboratory evaluation that I put there on the right. And any people who evaluate short stature will be familiar with the blood tests on the right and the disorders they identify if they are abnormal.

2016 PES GH Guidelines

The 2016 Growth Hormone Guidelines from the Pediatric Endocrine Society recommend that if a child meets auxilogical, ie, growth rate criteria concerning for growth hormone deficiency, has a pituitary defect on MRI (whether that be a tumor or malformation) or has a history of irradiation, and that person also has deficiency of at least 1 additional pituitary hormone, whether that be thyroid deficiency or cortisol deficiency, those persons meet the criteria for growth hormone deficiency and they do not need to have second tier testing with growth hormone provocative or stimulation test to establish that diagnoses.

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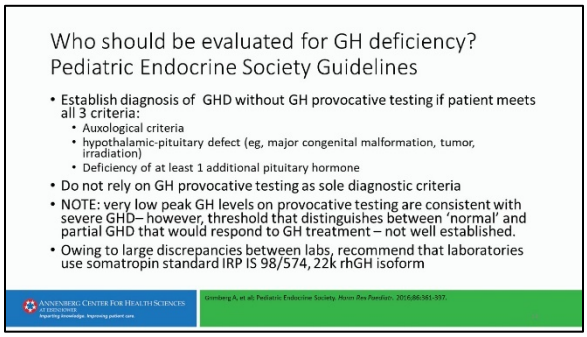
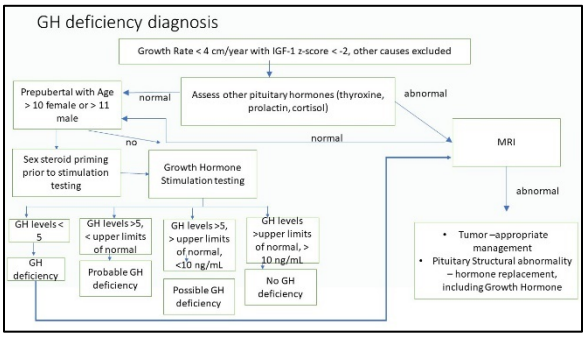




In most other cases, a growth hormone stimulation test will be needed to help assist in the diagnoses. The guidelines, which were based on the best available evidence at that time and since, could not specify a specific cut-off to identify growth hormone deficiency using provocative testing. So, therefore growth hormone results on the growth hormone stimulation testing are very open to interpretation and I will go through that on the next slide. And for these reasons, the guidelines recommend not to rely on growth hormone stimulation testing as the sole diagnostic criteria for growth hormone deficiency. It recommended using the auxilogical criteria and blood testing and making sure you're excluding other possible causes.

Because growth hormone assays can vary amongst labs, the guidelines also recommended that you use a reputable lab that uses a growth hormone or somatropin standard as listed here in their growth hormone assays so that your testing can be reproducible.

Diagnostic Algorithm for GHD

Being the practical practitioner that I am, and given that growth hormone stimulation tests are open to interpretation and the growth hormone guidelines could not and would not provide specific cut-offs, you know what do I do from a day-to-day basis in my clinical practice?

If a child has low growth rate who I see in my office and I have excluded other non-hormonal causes and if the child has normal pituitary hormones, I then proceed to growth hormone stimulation testing. If a child is of the ages listed, greater than 10 female or greater than 11 years male, I do do sex steroid priming. And why do I do this? So, sex steroid priming, especially in this age group, has been shown to increase the specificity of your growth hormone diagnoses and correctly identify children who, with growth hormone deficiency and who best benefit from growth hormone. Sex steroid priming is usually estrogen or testosterone, as is appropriate, given a week to 3 days prior to the date of the growth hormone stimulation testing.

Regarding the growth hormone stimulation testing, the growth hormone guidelines did not comment on which agents to use for growth hormone stimulation testing, they did state that 2 agents should be used. So, the common agents are arginine, clonidine, L-dopamine and glucagon. The guidelines, and many practices do not, there is no data on which 2 agents are the optimal combination to differentiate between growth hormone deficiency and no growth hormone deficiency. So, practitioners tend to use the 2 agents that they are most familiar with.

In interpreting the growth hormone levels post-stimulation testing, those levels less than 5 and

greater than 10 ng/mL are the most helpful because persons who do not achieve any growth hormone level greater than 5 are very high likelihood to have growth hormone deficiency and they do benefit most from growth hormone. Those with growth hormone values greater than 10, practitioners will agree do not have growth hormone deficiency, do not meet criteria for growth hormone deficiency.

Those with growth hormone values on stimulation testing that are above 5, but lower than the upper limits of normal for laboratory or between the upper limits of normal but less than 10 ng/mL on the growth hormone value, these are in the gray zone and this is very open to interpretation. It is not exactly clear. We don't have exact data on the response to growth hormone that these children have. Some children respond very well to growth hormone in these 2 groups; some do not and this is where the test is open to interpretation.

Again, if I diagnose growth hormone deficiency, whether by stimulation testing or by auxilogical criteria and other pituitary hormone deficiencies, these children get an MRI because [I want] to look for tumors or pituitary structural defects. Whether to do an MRI in the probable growth hormone deficiency or possible growth hormone deficiency groups is also controversial and very practitioner-dependent.

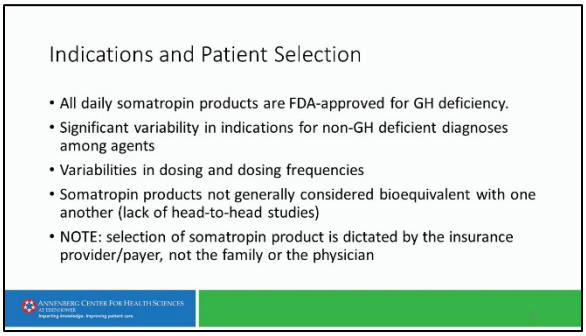
Summary

In summary, the differential diagnosis of attenuated growth is very broad and includes both hormonal and non-hormonal causes that must be investigated. The diagnosis of growth hormone deficiency can be difficult to distinguish between that and normal variants, such as constitutional delay of growth and puberty, so therefore, oftentimes, repeated assessment, a good family history can be necessary to differentiate between the 2. And oftentimes, growth hormone stimulation test may or may not be helpful and cut-offs for growth hormone deficiency, using these stimulation tests, are open to interpretation.

PEDIATRIC TREATMENTS OF GHD

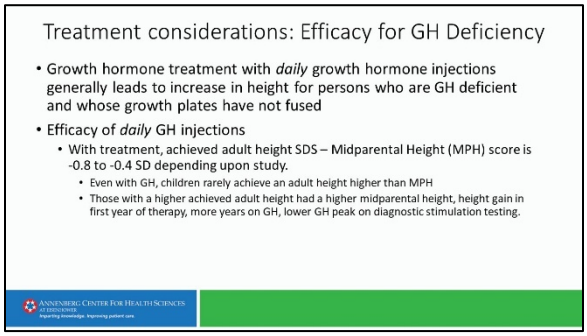
GH Indications and Patient Selection

Daily recombinant growth hormone has been approved by the FDA since 1985 and all daily injectable formulations approved by the FDA are approved by the FDA for growth hormone deficiency.



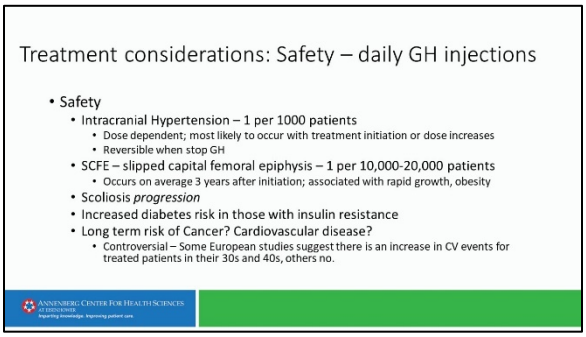
The recommended doses on the product information sheets for each brand actually vary. They can vary between dosage recommendations of 0.16 to 0.3 mg/kg/week. Actually 1 company, has received approval for puberty dosing up to 0.7 mg/kg/week. The other company formulations have not sought this FDA approval. Although different somatropin brands and products are generally not considered to be bioequivalent to each other by the FDA, shifting insurance company contracts between companies often dictate that brand changes occurs in clinical practice for which the practitioner nor the patient do not have a say. And this leads us to the fact that selection of somatropin product and company and provider is dictated by the insurance provider and third-

party payer, not by the family or physician, based on the cost and expense of growth hormone.



Studies of growth hormone deficient children treated with growth hormone, daily growth hormone, excuse me, unanimously show that growth hormone increases achieved adult height. The degree of adult height achieved varies slightly between studies.

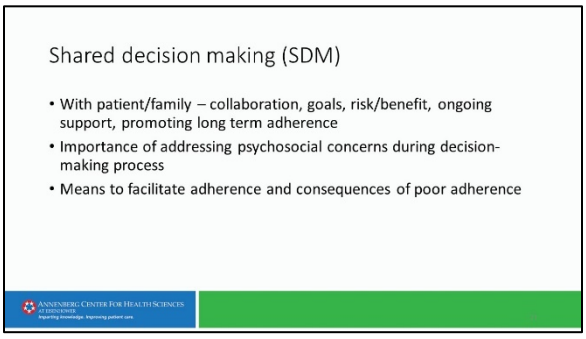
The product of achieved adult height minus, SDS minus mid-parental height, SDS score as reported here is the most useful comparator when comparing the results of the different studies that are in different countries. And these studies showed that in children who receive growth hormone for growth hormone deficiency, their adult height compared to their mid-parental height potential score was between 0.8 to 0.4, again depending on the study. Those with a higher achieved adult height had a greater genetic height potential, so a higher mid-parental height. They also had the most robust height gain in the first year of therapy, a longer duration of treatment, so more years on the growth hormone, and they also had a lower growth hormone peak on diagnostic testing. And these trends about who benefitted most from growth hormone were consistent across the studies that looked at adult height and are consistent across the nations.



To review what is known about the safety of growth hormone injections, intracranial hypertension and its incidence is slated here as is SCFE, slipped cap femoral epiphysis, and again mention the scoliosis progression and diabetes risk. And the uncertainty of the long-term risk of cancer and controversy about the long-term risk of cardiovascular disease decades after treatment.

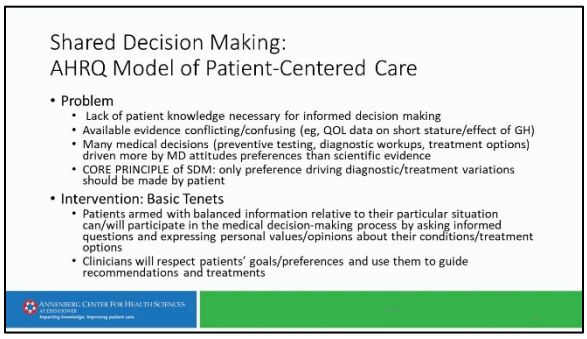
Shared Decision Making

The fact that the diagnosis of growth hormone deficiency is not black and white, it is very gray in some instances and the benefits are long term and may not be immediately seen by the child or the family.



This really brings in the concept of shared decision making on the decision to diagnose and treat growth hormone deficiency in a particular family. So, shared decision making is a concept

that, when a patient and/or family are armed with adequate information, they will bring their own values and goals and thoughts and risk-benefits to the conversation. They will actively participate in that medical decision making. You know, these patients will then feel vested in this process and vested in the treatment plan and then this will improve adherence and reduce the consequences of lower adherence and improve outcomes to the treatment regimen.



Given that shared decision making improves adherence and thus outcomes of the treatment plan, the Agency for Healthcare Research and Quality, the AHRQ, identified characteristics of clinical problems that particularly benefit from a shared decision-making approach. Characteristics of these thorny clinical problems include, you know, they're complex and often the nuances are difficult for patients to understand, the available evidence for the practitioner to synthesize for the patient can be conflicting and confusing even for the practitioner. And these 2 qualities leave space for the practitioner and provider biases and attitudes to filter in and drive recommendations. And these characteristics certainly embody the diagnosis and treatment of growth hormone deficiency, given the conflicting evidence of quality-of-life data on short stature and given the difficulty in the diagnostic work-up and establishing the diagnosis that may be driven by provider attitudes and previous practices.

A core principle of shared decision making is that, you know, in these types of thorny problems, a patient preference should be utmost in driving the diagnostic and treatment decisions and variations after being informed of relevant risks and benefits. And this core principle is based upon the tenets that patients are willing and want that balanced information and are willing to participate in the bidirectional conversation in this decision-making process. And they're willing to bring their own personal values and risks and benefits to this conversation in order to have a mutually beneficial outcome. And as expected, clinicians will respect the goals and preferences that patients bring to these conversations and use them to guide and make a mutual decision with the patient on the treatment plan.

SHARE

Seek your patient's participation

- Communicate that a choice exists and invite to be involved in decision

Help your patient explore and compare treatment options

- Discuss benefits and harms (and unknowns) of each option

Assess your patient's values and preferences

- Take into account what matters most

Reach a decision with your patient

- Decide together on the best option and arrange for follow-up

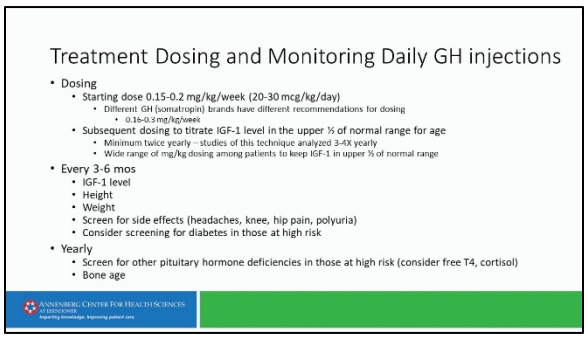
Evaluate your patient's decision

- Support your patient so treatment decision has a positive impact on health outcomes

A New Era in Relieving the Burden and Improving Health Outcomes of Children with Growth Hormone Deficiency

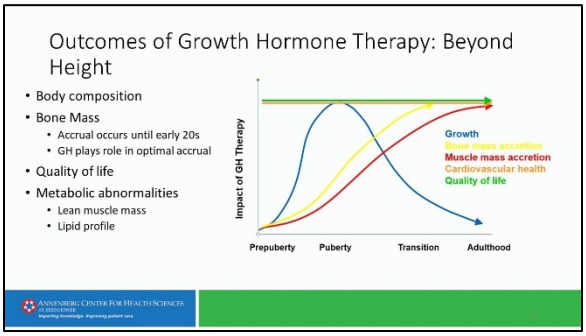
GHD Treatments: Overview

What are the treatment options for growth hormone deficiency? Well, up until very recently, it was daily growth hormone injections and the guidelines, these 2016 Pediatric Endocrine Society guidelines, suggested a starting dose between 0.15 and 0.24 mg/kg/week.



This was a synthesis, not only of the data, but also of the different somatropin brands will have different recommendations for initial dosing and this was a synthesis of the available data. You know, subsequent dosing after the initial mg/kg weight-based dosing has been suggested to be titrated to IGF-1, to the upper half of normal range. Studies have, in the early 2000s, shown that children with diagnosed growth hormone deficiency over a 1-year period, if the children who were able to titrate the IGF-1 up to the upper half of normal had higher growth velocity than those who IGF-1 was in the lower half of normal range. What was interesting with this study is that there was a very wide range of weight per day still seen among patients to keep this IGF-1 in upper half of normal range. Some children required that dosing of 0.3 mg/kg/week to achieve that IGF-1 level and some needed that lower end. So, it was a highly individual differences and this is a way to individualize therapy between your patients and achieve the best outcomes.

The suggested frequency for safety and lab monitoring is also stated in this slide. Again, every 3 to 6 months, however (often) the patient with growth hormone deficiency is seen, you should get a height and weight as this monitors your growth response to your therapy, IGF-1 not only to target in the upper half of normal range for age but can also be used to monitor adherence as it is directly related to growth hormone dosing, the IGF-1. And each visit, you should screen for side effects and again, screening for diabetes in those at risk, whether with symptom screening or whether with specific diabetes screening with a glucose or A1C. For yearly recommendations, screen for pituitary hormone deficiencies in those at high risk, specifically a free T4 and cortisol. Growth hormone does increase free T4 to T3 conversion, hence that recommendation to monitor free T4 in people, children on growth hormone. And obviously, a bone age to help with predictions on adult height.

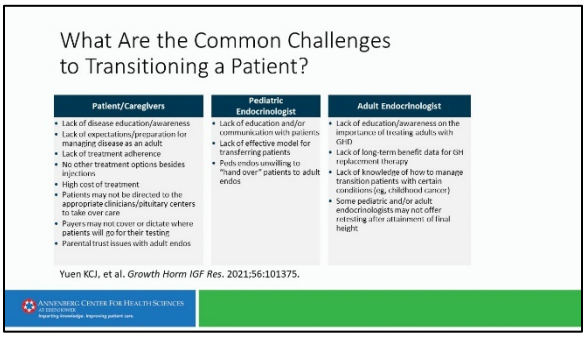


This systemic review looked at 6 observational studies of children treated with growth hormone, no matter the indication, whether that be growth hormone deficiency, Turner syndrome, Prader-Willi syndrome or SGA-related short stature, and they measured it here and it's based upon either self-report or returned or unused vials and medications or a

specific device. So, of these 6 studies, rates of nonadherence varied between 7% and up to 70% in a different study. So, within this systematic review, these authors identified 22 different factors, you know, that could contribute to nonadherence. And these factors include their physical capability, uncomfortableness with the injection or pain on the injection or even concerns about inadequate training on injection, they didn't feel comfortable, dissatisfaction because they are not growing and they didn't want to do it anymore and little things, like lifestyle disruptions, such as a vacation or a move that they didn't take the growth hormone anymore because of these mild or these lifestyle disruptions. So, clearly there's a myriad of reasons and barriers to daily injections that makes it difficult for families and for patients to be adherent to their daily growth hormone injections.

GHD Treatments: Considerations

What are the outcomes of growth hormone therapy? It is very important to know that the child goes through different stages in life. Once they achieve puberty, they transition over to adulthood, you can see that the main goal of growth hormone therapy is not so much growth induction, but more of metabolic reversal of this condition. So, you can see that growth hormone can improve the body composition, induce improvements in bone mass, particularly when they are in the early 20s, and also quality of life is also an important factor and also metabolic abnormalities, particularly lean body mass and also improvement in glucose and lipid profile.



The duration of growth hormone therapy is divided into the transition stage where the child who has reached final height, where the decision is then to consider stopping growth hormone at that particular point in time and reevaluation for persistent growth hormone deficiency is required at this stage. For males, when the growth hormone rate is less than 3 cm per year and a bone age of 17 is typically when the adult height or the final height is reached. For females, growth rate of less than 3 cm a year and bone age of 14.

Once these milestones are achieved, then retesting is recommended in most patients, particularly for patients who have 2 or fewer pituitary hormones. Then the likelihood of having persistent growth hormone deficiency is roughly between 30% to 70% of patients and, in this situation, repeat testing is definitely recommended. This typically tends to occur, or is recommended for repeat testing, at least 1 month after growth hormone has been discontinued.

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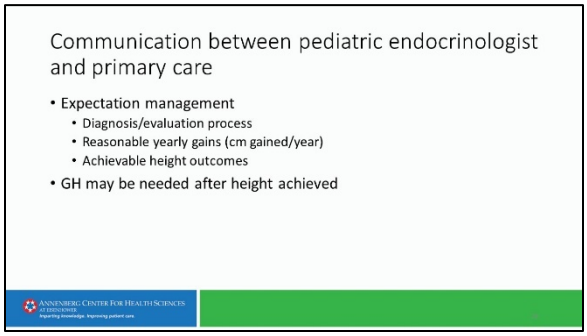
For those patients who have multiple pituitary hormone deficiencies, meaning at least 3 or more pituitary hormone deficiencies and a low IGF-1, in this situation, growth hormone deficiency tends to persist into adulthood and therefore repeat testing is not necessary for these patients. Otherwise, for all other patients, repeat testing is recommended to assess the persistence of growth hormone deficiency moving into adulthood.

Transitioning From Pediatric to Adult Care

When a patient transitions over from pediatric to adult services, there are several common barriers and challenges that face both the patients, caregivers and also the providers, be it pediatric endocrinologists or adult endocrinologists.



Several factors that actually come into play that is relevant for patients and caregivers, such as those patients who have lack of disease education or awareness. In other words, patients are not quite sure and they don't fully understand the importance of growth hormone deficiency and how growth hormone works and what it does to their bodies. There's also a lack of expectation and preparation for managing these diseases in adulthood and, as a result, patients may not think now that they have gone into adulthood, that continuing growth hormone is necessary simply because they think that they are fully grown.

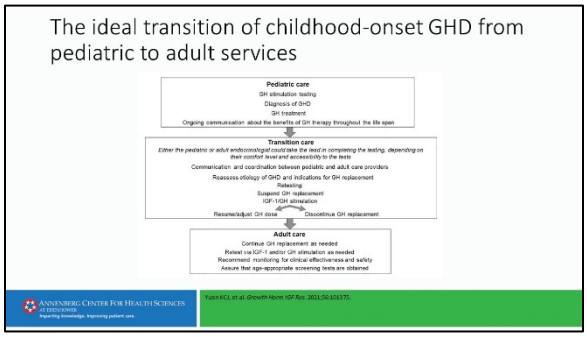
Treatment adherence is also a big problem, not only in children with growth hormone deficiency, but also in adults and certainly when they have finally reached the transition period where they know that growth hormone can be stopped, convincing them to go back on growth hormone, if they are truly growth hormone-deficient, may be difficult because they may not see the benefits and the relevance of continuing daily growth hormone. So, treatment adherence could be a problem in that situation.

Some patients want to go on growth hormone, but not necessarily injections, and so they would be asking for other options that may be available to treat them and, certainly, in this, at this moment in time, growth hormone is only administered only by injections and there is no other way that growth hormone can be administered. Growth hormone is also an expensive treatment and it's also a time where insurance changes. Some of these young adults may be going to college, they may be moving out of town, out of their families' homes and they may also not have insurance or lose their insurance, so that may be a problem as well.

Patients may not be directed to appropriate clinicians and they may not have the proper education as to who they should turn to when they have moved out of town and so certainly this could be a problem establishing connections with new providers. Payers may not cover these patients when they move to a different state, so that's also a problem. And there's also parental trust issues with adult endocrinologists because they have established a good rapport and a relationship with their pediatric endocrinologist all these years. From the pediatric

endocrinologists' standpoint, some pediatricians may lack the education or may not communicate very well to the patients the importance of retesting these patients for potential growth hormone deficiency and so they may not be tested. And there's also a lack of transfer model for these patients to be transferred from the pediatric services to the adults and ped-endos also may want to continue treating these patients because they have been treating these patients for many years and there is a degree of unwillingness for them to hand over these patients to the adult colleagues.

For adult endocrinologists, there's also a lack of education, maybe, about the true benefits of growth hormone use in adults. There's also certainly a lack of long-term beneficial data and safety data as well of growth hormone replacement. Some pediatric and adult endocrinologists may not be able to offer their facilities for retesting and certainly this is a problem in an office setting where growth hormone stimulation tests may not be available for some providers because it is difficult to conduct such tests in an office.



Communication is a key part in this transition between a pediatric endocrinologist and the primary care. Firstly, in setting the expectation of the importance of diagnosis of persistent growth hormone deficiency as they go into adulthood and it's also important that once they have achieved reasonable gains in their final height and height outcomes, that the treatment doesn't necessarily stop there because there are still metabolic changes that can continue to occur moving into them being a young adult. So, growth hormone may still be needed, even after final height is achieved.

Ideal Transition from Pediatric to Adult Care

In an ideal setting, how do you transition a childhood-onset growth hormone deficient patient from the pediatric to the adult services? Ideally, from the pediatric standpoint, once the patient has stopped growth hormone treatment, they could be given a break of at least 4 weeks and then they could be retested to see if they continue to have growth hormone deficiency. Ongoing communication at this stage is critical to emphasize the benefits of growth hormone therapy throughout the life span. If the patient continues to have growth hormone deficiency as confirmed by the retesting of growth hormone stimulation tests, then they could be transitioned over to the adult services and, at this stage is where either the pediatric or the adult endocrinologist could take a lead role in educating the patient about the implications of their test results and also, moving forward, how to resume growth hormone dosing. Or, if they are found to be growth hormone sufficient after the growth hormone stimulation tests, then to educate them that they could stay off growth hormone indefinitely, given that they are no longer growth hormone deficient in the transition stage.

But for those patients who are persistently growth hormone-deficient moving into adulthood, growth hormone replacement should be restarted and periodic IGF-1 testing should be undertaken to maintain the IGF-1

levels within the normal range and indeed, the patient needs to be monitored for clinical effectiveness and also to be educated to look out for any potential side effects associated with this treatment.

SUMMARY

In summary, daily growth hormone has been shown, in multiple studies now, since its inception and its approval over 25 years, that it has a proven track record for efficacy and safety for both childhood-onset and adult-onset growth hormone deficient patients. For the best outcomes, growth hormone treatment is not a treatment that you can use for a few months. This treatment requires multiple years of therapy and, indeed, patients need to be educated that the expectation is that when they go on growth hormone, it is a treatment that is over a period of many years and it's not just over a few months. Response to therapy may vary, just like any medications, among a variety of patients. So, it is important for the provider to discuss about the expectations, about the potential outcomes and that treatment doses may need to be changed accordingly, depending on response to therapy.

It is also extremely crucial that appropriate confirmatory testing is undertaken at the transition stage. This should hopefully provide a seamless growth hormone replacement therapy for those patients who continue to have growth hormone deficiency moving forward into adulthood. A clearly structured transitional protocol or pathway is important between the pediatricians and the adult endocrinologists in order to provide useful and practical guidance for those pediatricians who have these patients and to establish best practices when these patients are transitioned over. The hope is that these patients are transitioned seamlessly over into adult services.

RECOMBINANT GROWTH HORMONE THERAPIES

GHD TREATMENTS: OVERVIEW

Let us discuss the available recombinant growth hormone treatments and the types of factors to consider for treatment selection between approved products. For these products we talk about indications, the frequency of administration and, importantly, the tolerability and safety profile of these medications.

AVAILABLE GHD TREATMENTS

There are several brands of growth hormone available, genotropin, humatrope, norditropin, nutropin, omnitrope and saizen.

Somatropin Products Available in the United States for Pediatric Growth Hormone Deficiency

	Indications							Frequency of Administration
	GHD	TS	ISS	PWS	SHOX	SGA	NS	
Genotropin	✓	✓	✓	✓		✓		6-7 days/week
Humatrope	✓	✓	✓		✓	✓		Daily
Lonapegsomatropin	✓							Once weekly
Norditropin	✓	✓	✓	✓		✓	✓	6-7 days/week
Nutropin	✓	✓	✓					6-7 days/week
Omnitrope	✓	✓	✓	✓		✓		6-7 days/week
Saizen	✓							Either 3 alternate days, 6 days/week, or daily

GHD, growth hormone deficiency; TS, Turner syndrome; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SHOX, short stature homeobox-containing gene; SGA, small for gestational age; NS, Noonan syndrome

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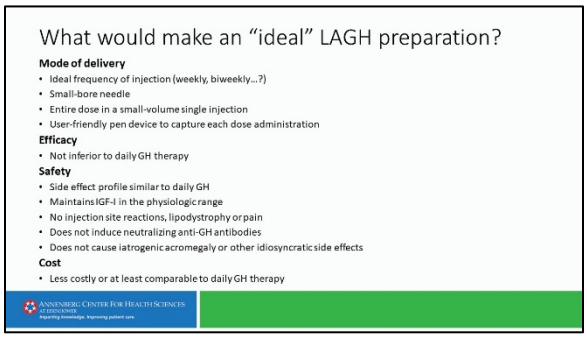
They are all daily-administered growth hormone preparations. Lonapegsomatropin is the newly-approved, FDA-approved long-acting growth hormone preparation which is administered once weekly. That is approved in patients with childhood growth hormone deficiency, so it is approved in the pediatric cohort. But the other daily growth hormone brands are approved also not only for growth hormone deficiency, but also for Turner syndrome, idiopathic short stature, Prader-Willi, SHOX, SGA and Noonan syndrome. So, there are other indications for use of daily

growth hormone, not only for growth hormone deficient patients alone, currently in the market.

Long-Acting Growth Hormone Preparations: Overview

You may have read also that recently there have been a lot of studies on long-acting growth hormone preparations. So, the question is why do we consider long-acting growth hormone preparations? This is because there are issues with daily growth hormone injections, particularly the fact that growth hormone that is injected daily can be inconvenient, painful and distressing to both patients and caregivers. There's also distinct lack of information as to perceived effects of growth hormone. Many patients assume that growth hormone is only used to achieve growth, but they are not aware that growth hormone is also an important hormone to regulate their metabolic profile and to improve their metabolic parameters as well. Because of the fact that it is inconvenient and painful, there's a high number of patients, a high degree of patients, both in adults and children, who are nonadherent and the hypothesis is that, by decreasing the injection frequency, long-acting growth hormone preparations may improve the quality of life and the adherence. And, thereby, when adherence is improved, clinical outcomes can be improved as well. Now, clearly, this needs to be proven, but this is the current working hypothesis.



What would make an ideal long-acting growth hormone preparation? I think a long-acting growth hormone preparation that is ideal would include the fact that it's delivery should either be at least weekly or even every 2 weeks or even every month. And this hopefully would reduce the number of injections that the patient needs to perform. The needle should be very small, and the smaller the needle, the more the likelihood that the injection would be painless. The entire dose should be administered in a small volume, single injection. Again, volume plays an important part because the higher the volume, the more painful it can be for the patient. The injection pen device could be in the form of a very sophisticated, yet user-friendly pen device in order to capture and to enable the accurate dose to be administered for each dose as well.

In terms of its efficacy, it should not be at least inferior to daily growth hormone therapy. It should be at least the same or if not better than daily growth hormone therapy. In terms of safety, it should be at least as safe as daily growth hormone. It has the ability to maintain IGF-1 in the physiological range. The injection sites should not cause any problems, like pain, lipodystrophy or infections. It should not induce any neutralizing anti-growth hormone antibodies and it should not cause the opposite effect, which is iatrogenic acromegaly or other idiosyncratic side effects. And finally, the cost, again a very important part, it should be at least comparable to daily growth hormone or less costly, and that is always very helpful for patient accessibility.

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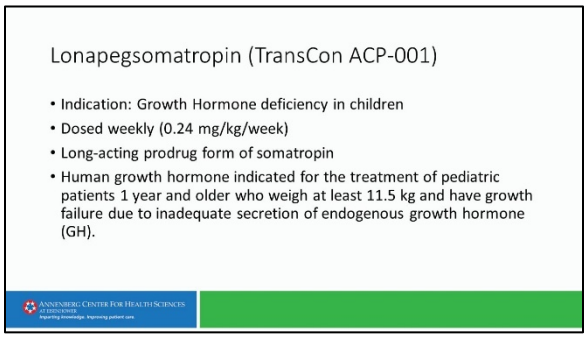
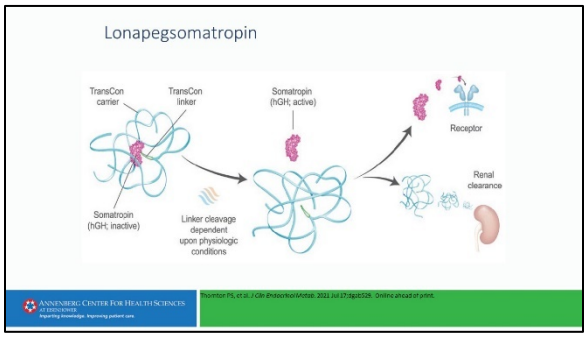
LONAPEGSOMATROPIN: THE FIRST LAGH

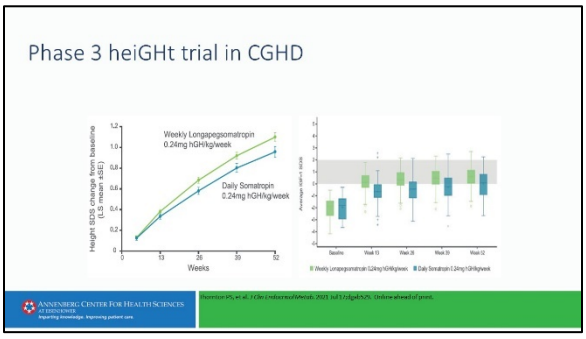
Lonapegsomatropin which is the newly-approved, long-acting growth hormone preparation that is used now for growth hormone deficiency in children. It is currently dosed at 0.24 mg/kg/week and it is indicated for treatment of pediatric patients who are 1 year old or older, weigh at least 11.5 kg and who have documented to have growth failure due to inadequate secretion of endogenous growth hormone.



Lonapegsomatropin, the molecular structure looks like this. You can see that there is a native growth hormone molecule that is attached to a very sophisticated TransCon carrier through a linker that is cleaved-dependent upon physiologic conditions.



This compound is carried through the circulation, and when it arrives to the growth hormone receptor it releases the growth hormone molecule to attach itself to the receptor. And because it's cleared in the kidneys, the TransCon linker and the TransCon carrier is effectively cleared in the kidneys, but because it's carried on by the TransCon linker, it actually has the ability to provide the growth hormone molecule to the receptor and prolongate its actions at the level of the growth hormone receptor.



26:16.9 This is a very interesting study. It's a pivotal study whereby the lonapegsomatropin was compared to daily growth hormone preparations and in the phase 3 heiGHt trial that was published about 6 months ago. And what they found was that there was an improvement in the height SDS between the long-acting growth hormone much more so compared to daily somatropin at the end of 1 year of treatment. And during that year, you can see that the average IGF-1 SDS was achieved at a somewhat slightly higher (rate) than daily growth hormone.

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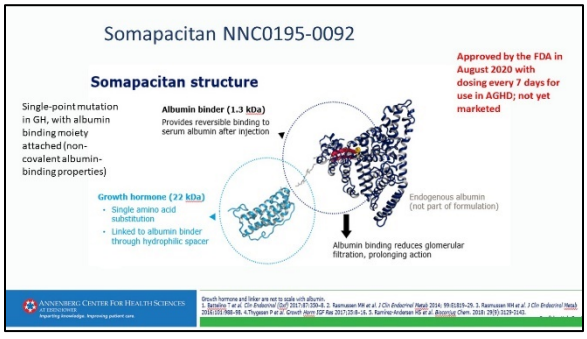
NEAR-TERM LONG-ACTING GROWTH HORMONE THERAPIES

PROLONGING BENEFITS OF GH INJECTIONS

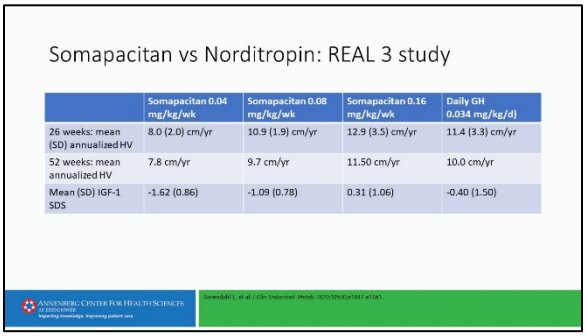
What about other long-acting growth hormone preparations? Well, there are other ways of prolonging the actions of growth hormone. There is the depot technology where the growth hormone molecule is delayed in terms of its absorption in the subcutaneous space and the delay is formed by incorporating the molecule into microspheres. There's also the pegylation method, or the prodrug method, where the growth hormone molecule is pegylated and, by pegylating the molecule, there is a slower clearance from the circulation, thereby increasing the duration of action of the growth hormone. There's also growth hormone fusion proteins whereby there are synthetic polypeptides and naturally occurring proteins that actually attaches itself again to prolong the actions of growth hormone. And finally, there's also a new technology where they combine the growth hormone molecule to endogenous albumin which is a protein in the blood and by modifying the binding to this protein, it actually prolongs the actions of growth hormone, on the growth hormone receptor.

SOMAPACITAN



Somapacitan is one such compound where it's bound to the endogenous albumin and you can see here the growth hormone molecule, a 22 kDa molecule, that is attached to the albumin via an albumin binder which is 1.3 kDa and when this compound is attached—when the growth hormone molecule is attached to the albumin molecule—it actually increases the molecule substantially, the molecular weight, and thereby, by increasing this molecular structure, it reduces the glomerular filtration of the drug and therefore it hangs around longer and that's how it prolongs the action of growth hormone.

It was approved by the FDA in August 2020 for use in adults with growth hormone deficiency. It is administered every 7 days. However this compound, although it is approved, is not marketed yet. So, it's still not made available to the public.



	Somapacitan 0.04 mg/kg/wk	Somapacitan 0.08 mg/kg/wk	Somapacitan 0.16 mg/kg/wk	Daily GH 0.034 mg/kg/d)
26 weeks: mean (SD) annualized HV	8.0 (2.0) cm/yr	10.9 (1.9) cm/yr	12.9 (3.5) cm/yr	11.4 (3.3) cm/yr
52 weeks: mean annualized HV	7.8 cm/yr	9.7 cm/yr	11.50 cm/yr	10.0 cm/yr
Mean (SD) IGF-1 SDS	-1.62 (0.86)	-1.09 (0.78)	0.31 (1.06)	-0.40 (1.50)

There is a nice study looking at somapacitan vs daily growth hormone norditropin. The study is called REAL 3 where they looked at 3 different doses of somapacitan in comparison to daily growth hormone. And, as your doses are gradually increased of somapacitan, the annualized height velocity increases and the somapacitan dose 0.16 mg/kg/week is very comparable to the daily growth hormone administration. And, in fact, after 52 weeks of administration, the height velocity per year is the highest in the higher dose of somapacitan compared to the lower dose, suggesting there's also a dose-dependent effect as well.

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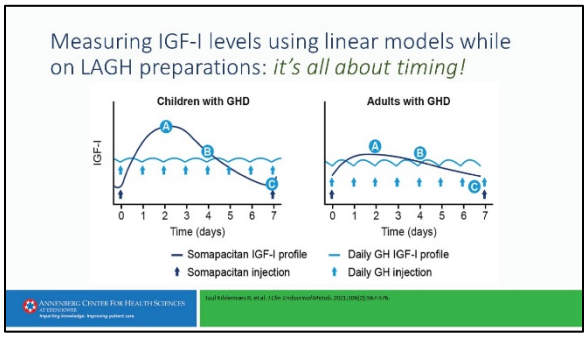
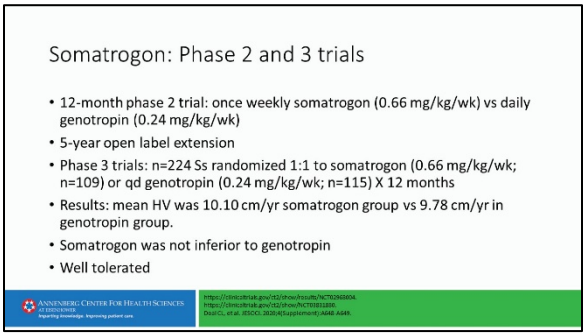


The problem is that when you are giving growth hormone once a week, the question then becomes when do you measure the IGF levels? Here is a linear model of how IGF-1 should be measured in relation to when the injections are administered. So, for example, if the injections are administered every 7 days, the fact that if you're measuring it at day 2 would indicate that this is the peak growth hormone level, whereas at day 4 would be the average or the mean growth hormone or the IGF-1 level, I should say. And then if you measure it at day 7, it would be the trough level.

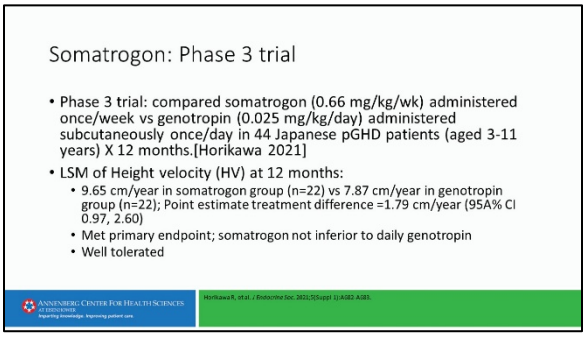
It is a little bit more pronounced in children, as you can see in this slide on the left-hand side, the peaks and the troughs compared to adults. And I suspect this is probably related to the fact that children typically are on much higher doses than adults, which may suggest that this is the reason why the IGF-1 levels tend to be higher at the mid-range compared to adults.

SOMATROGON

Another long-acting growth hormone preparation that is also actively being studied is called somatrogon or MOD 4023. This is a long-acting recombinant growth hormone where there is an amino acid sequence of growth hormone together with 3 copies of carboxy-terminal peptide or CTP of the human chorionic gonadotropin molecule that is attached to this hormone.



It is being developed as a once-weekly treatment and here are some of the data of the phase 2 and phase 3 trials that are currently being undertaken. There is a 12-month phase 2 trial where the once-weekly somatrogon is compared to the daily genotropin and this is a 5-year, open-label extension study. The phase 3 trial where there are 224 short stature patients that are randomized 1:1 to somatrogon vs daily genotropin over 12 months. The results indicate that the mean height velocity was 10.1 cm per year of somatrogon vs 9.8 cm per year for genotropin group. So, the mean height velocity was comparable between the somatrogon vs the genotropin group, indicating that there was no inferiority between somatrogon and genotropin. During the trial, somatrogon was also overall well tolerated.



In a recently published, phase 3 trial looking at the effects of somatrogon vs daily genotropin in Japanese pediatric growth hormone deficient patients, there were 44 patients that were recruited between the ages of 3 to 11. They were treated for 1 year and the data indicate that somatrogon induced 9.7 cm per year of height vs 7.9 cm per year of genotropin. So, the point estimate treatment difference was about 1.8 cm per year, indicating that this study met its primary endpoint of the fact that somatrogon was not inferior to daily genotropin and was also very well tolerated in this group of patients.

Biomarkers of Daily vs LAGH

What are the biomarkers of daily vs long-acting growth preparations in terms of are there any differences? We know that daily growth hormone is not truly physiological to growth hormone secretion, to endogenous growth secretion. And so, if the daily's not physiological, definitely the long-acting preparations are definitely not physiological as well. So there will be differences in terms of the daily pharmacokinetics and pharmacodynamics of growth hormone preparations vs long-acting growth hormone preparations. And we are talking about the duration of growth hormone exposure, so the daily would be hours a day vs days per week for the long-acting. There is the duration of exposure, meaning you will see that, for long-acting growth hormone preparations, there will be a peak and there's also a trough of IGF-1 levels that perhaps you may not see that so much in daily growth hormone preparations. There are also slight differences between the relationship of growth hormone and IGF-1 levels because of the fact that the long-acting growth hormone preparation hangs around longer and therefore growth hormone levels typically tend to be high, to be elevated longer than daily preparations. And there's also the issue of tissue distribution because the long-acting growth hormone preparations are made up of larger molecules so the question is: are there going to be any differences in tissue distribution of growth hormone? Simply because the growth hormone molecule is modified, will there be differences in where the tissue, growth hormone is distributed in different tissues?

Appropriate Candidates and Outstanding Questions Regarding LAGH

The question is then if you have long-acting growth hormone preparations made available, what types of patients would benefit most? I think patients that would benefit most would be those that are about to start growth hormone, but then they have indicated that they are a little bit apprehensive about the injections. These types of patients are likely to be nonadherent and so they may definitely benefit from long-acting. Patients who are already on many other injections, like insulin injections, testosterone injections, they may benefit from having a lesser frequency of growth hormone injections. Patients who may have difficulty self-injecting or may be apprehensive of self-injecting but are willing to start on growth hormones, these patients may also be considered for long-acting growth hormone. There's also those patients who are already on daily growth hormone injections, but are currently struggling to keep up with giving themselves their injections daily and certainly these are also patients that we can consider for long-acting growth hormone.

However, long-acting growth hormone, just like any new drug, still has many questions. How to appropriately and optimally start these patients and how do you adjust the dosing? When is the best time to measure IGF-1 levels? And is it the same for all preparations, taking into consideration that different growth hormone

preparations have different molecular structures? Would long-acting growth hormone preparation, given the changes in the molecular structure, cause tachyphylaxis or down-regulation of growth hormone receptors, especially given its long-term use? Will its effects be durable over long term? Can they penetrate tissues equally between different growth hormone preparations? Will there be long-term metabolic consequences, given that it can induce elevations in growth hormone for a few days during the week where in between it, the week that it's injected? Are they cost-effective? Will they eventually prove to improve adherence and outcomes? And will it be as safe as daily growth hormone? So, these are still questions, open questions, that need answering.

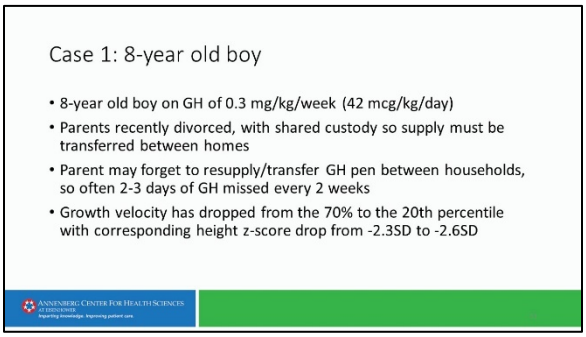
SUMMARY

Long-term, long-acting growth hormone preparations have been and are currently being developed, but it is important to note that they all have different molecular structures. Short-term studies that have shown long-acting growth hormone preparations are noninferior to daily growth hormone in terms of efficacy and safety, but long-term studies are still needed to show this effect. They are definitely more convenient than daily growth hormone injections because they're administered once a day, once a day vs once a week. And although it has the promise to improve adherence and long-term outcomes, long-acting growth hormone preparations still need to be proven in large, prospective clinical studies.

CASE STUDIES

CASE 1: 8-YEAR-OLD BOY

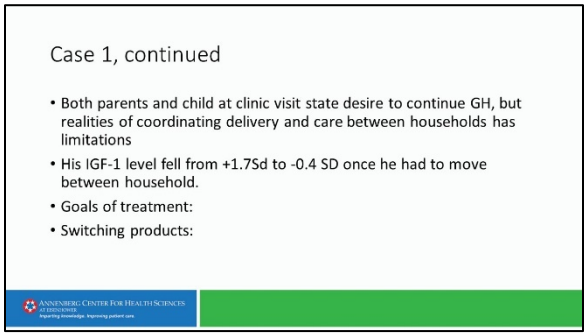
The first case is an 8-year-old boy who is already on daily growth hormone at an approved dose of 0.3 mg/kg/week and divided over 7 days.



He's on it 7 days a week. The parents of this child have recently gone through a divorce and, with the shared custody, the child alternates between home each week. So, their supply must be shared and transferred between these homes, with the child. And parents do state that they do forget to, you know, transfer the growth hormone pen in between households, so they do admit that they're missing days of growth hormone. They estimate maybe 3 days every 2 weeks.

When you see the growth charts for this child, you notice that he was previously responding well to growth hormone, but since the family change his growth velocity has dropped from the 70th percentile to the 20th percentile and corresponding z-score also dropped. Height z-score also dropped. And, you know, considering his response in the first year of therapy, this is now year 3 of therapy, both parents are invested and they want to continue growth hormone, but they state that, you know, the realities of our current life and coordinating delivery, we do miss, and it's been hard. And we're trying our

hardest, but it's been hard because of the realities of life.



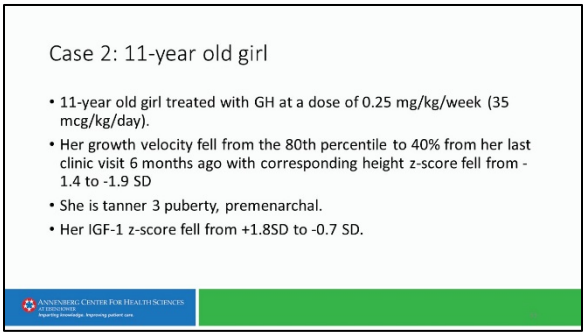
His fewer growth hormone injections plus the fact that his IGF-1 level fell as well, from when you last saw him. So, in thinking about the goals of treatment and the fact that this 8-year-old child, whom had an initial robust response to the first year of growth hormone, daily injectable, and through circumstances uncontrolled by this child and through this family, is really having problems with adherence. And therefore, this lack of adherence is preventing them from meeting, potentially meeting, that long-term goal of increased adult height. So, now in the past, your options were to, you know, work with the family to think of ways to remember to transfer the pen and coordinate deliveries. With the long-acting hormone, now you can offer them a weekly hormone which can be present at 1 parent's house and consistently given. And, and as stated before, the technique of switching from daily growth hormone to once a week is you need at least 8 hours in between that last daily growth hormone injection and the first weekly injection.

As far as monitoring treatment, in the lonapegsomatotropin studies, the reported IGF-1 was a, you know, average, they averaged out the 7 days and after creating models. So, in practicality, what are you going to follow over time? Will you be able to possibly get a day 4 consistently on this patient? I would recommend that you try to consistently get an IGF-1 at a consistent time post-injection to help monitor therapy. And again, we don't know whether the average IGF-1 is best used to monitor safety and efficacy or if it's the peak or the trough. And that data will come in post-marketing studies.

In conclusion, in this thorny situation where everybody has a desire to continue growth hormone and the practicalities of life it is, you know, very difficult, you now have an option for long-acting growth hormone which itself has some barriers as far as, for the practitioner, how am I going to interpret growth, IGF-1 levels, but it is an important option for the family.

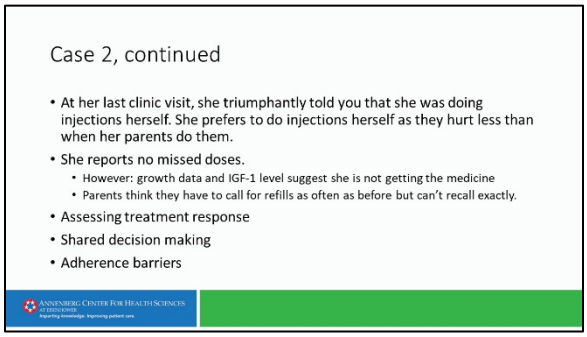
Case 2: 11-Year-Old Girl

The second case is an 11-year-old girl, also on growth hormone since age 8. She's been treated at a mid-dose with a good response and her growth velocity is in the 80th percentile.



You noted that the growth velocity, when you looked at her height data, fell to 40th percentile from 6 months ago and the corresponding height z-score fell as well. And this is ultimately concerning because she is in tanner 3 puberty where she should be having a very robust growth spurt, so this is equally concerning. And her

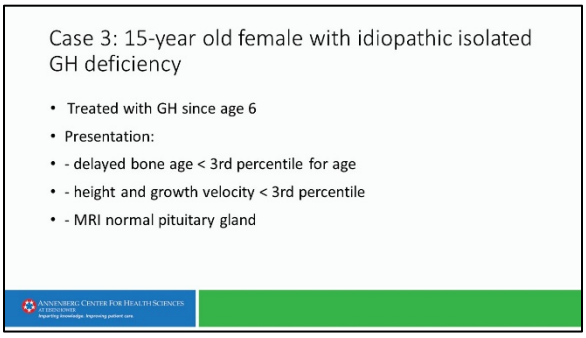
corresponding IGF-1 z-score fell, so you have multiple points of data that, gosh, is she getting her growth hormone at this very crucial time when she's undergoing the prepuberal growth spurt?



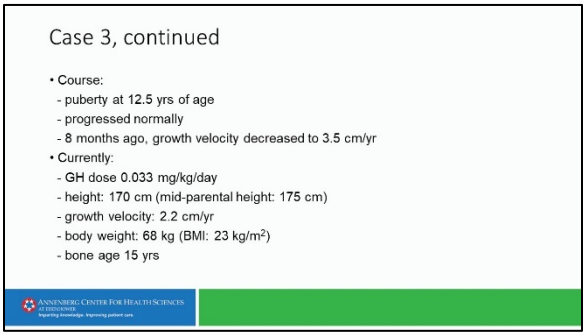
You note that last time you saw her, she was very proud of herself because she was finally doing injections herself and she liked to do it because they hurt less than when her parents did them. And when you see her today, she's like, yeah, I'm giving myself the growth hormone, I do it in my bedroom because I do it right before I go to bed and you say, okay. The parents are trying to give her some autonomy and have not been monitoring or can't recall if the refills are as often as before. So, again, you have a suspicion of nonadherence due to the fact that you have an 11-year-old with good intentions to want to do things by herself, but developmentally doesn't organize herself to do it. So then, again, you would discuss with this girl and this family that during this very crucial time of the puberal growth spurt, it's very important to maintain that growth they've worked so hard on before, starting at age 8. How can you improve your growth outcomes and improve adherence? And this is again a situation in which the long-acting growth hormone may be a nice option for these families when we did not have this option before. And because the long-acting growth hormone is itself an auto-injector, very similar to the daily growth hormone injections, it is something also maybe this child's sense of autonomy can still be there because she can auto-inject herself.

Case 3: 15-Year-Old Female

The third case is a 15-year-old female who presents with idiopathic isolated growth hormone deficiency, initially diagnosed at the age of 6 years old.



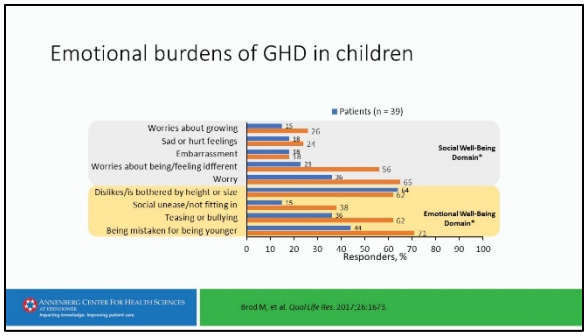
Following her diagnosis, she was then treated with growth hormone replacement on a daily administered [basis] since then and presentation at age of 15 was that there was a delayed bone age in the third percentile for age and there was a height and growth velocity that also was within less than the third percentile and MRI revealed a completely normal pituitary gland.



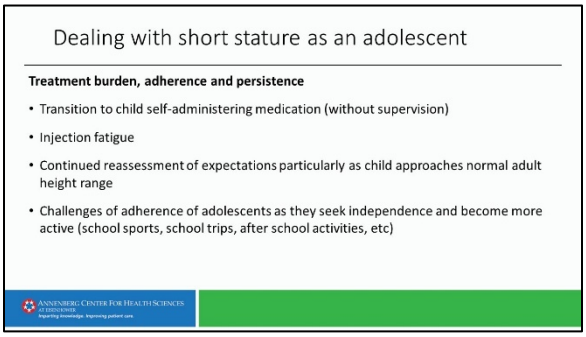
Over the course of treatment with daily growth hormone, she achieved puberty at age of 12.5

years. She appeared to progress normally, but 8 months prior to presentation, it was noted that her growth velocity started to decline. On presentation, she was on a daily growth hormone dose of 0.033 mg/kg. Her height at that time was 170 cm and note that her mid-parental height was 175 cm. At that time, on presentation, her growth velocity had dropped to 2.2 cm a year. Her body weight was 68 kg with a BMI of 23 kg/m^2 and her bone age at that time was 15 years.

This is a very typical case that we see where there is an apparent drop in growth velocity and it turns out that this patient, over the last 10 months to 12 months, has not been able to keep up with her daily growth hormone injections and it is reflected with a drop in the growth velocity. And so, for this patient, she was counseled on how to administer her growth hormone daily and how to keep up on that. And it would appear that she would be a good candidate to be considered for a long-acting growth hormone preparation.

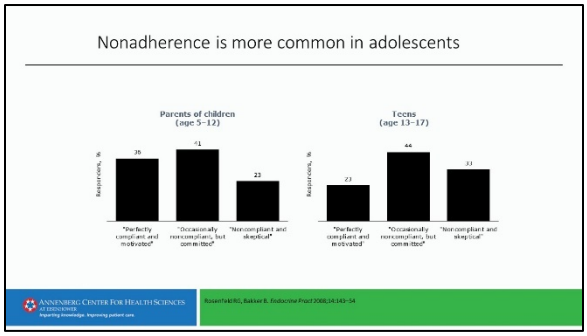


Given the situation of short stature, there is a high degree of psychosocial adaptation that is associated with short stature. Importantly, there are several factors that may affect psychosocial adaptation among those who present with short stature. It is shown that males tend to be more affected than females and also that the presence of a younger, but taller, sibling. The fact that they are being perceived and treated as younger because they look younger and they look shorter than their chronological age. There is also some suggestion, especially the genetic causes that not only that they're growth hormone deficient, that they may have also lower intelligence. There's also a good number of patients that come from lower family socioeconomic status. And very importantly, in this age group, when you're short, they find it difficult to be accepted into some peer group activities and that becomes a problem for acceptance into school and also together with your friends, as well and doing well in school.

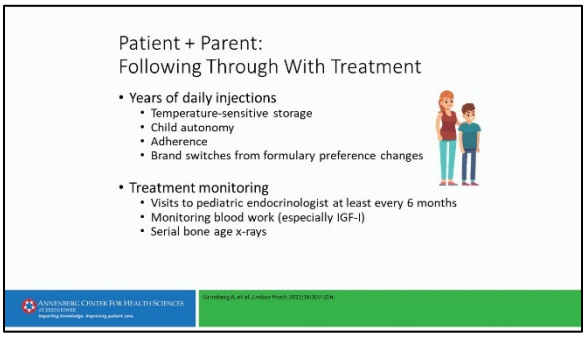


As you can see here, there's a variety of factors that are associated with emotional burdens of growth hormone deficiency in children. This is a study by Brod, published about 5 years ago, and they found that both not only patients, but also caregivers, actually have reported that a number of factors can actually affect the patients from an emotional standpoint. They worry about growing. There's also a feeling of embarrassment and depression, worry about being different to their peers. They do not like how they look. They feel socially uneasy and they do not find themselves fitting in very well. They are subject to being teased or bullied by their taller peers. They're often being mistaken

for being younger in their group. So, these are factors that actually affect many of these patients.



What about dealing with short stature as an adolescent? There are many factors, but the main goal is the treatment burden, adherence and persistence. Transitioning the child with self-administering medication without supervision always has been a challenge. A child has to take on board the responsibility of giving himself or herself the injections daily and that can be challenging, especially when they miss an injection and they don't necessarily see any negative effects after missing an injection or 2, so they may not necessarily want to continue giving themselves injections. Many of these children also complain of injection fatigue. They continue, there's also a continued reassessment of expectations, particularly as they're growing and as the child approaches normal adult height range. They want to be accepted with their peers, but at the same time they are finding it hard to keep up with the injections. There's also other factors in life that also distracts them from the injections, particularly if they're having many school trips, they're having school exams, they're having assignments and school activities. These are things that actually can affect the adherence and make them less likely to be able to keep up with the daily injections.



This is a study by Ron Rosenfeld, published about 13 to 14 years now, and it's actually a very nice study where they compared both children and teenagers and they found that certainly between 60% to 70% of children and teenagers are noncompliant, indicating that there is a high proportion of these patients who are actually not able to keep up with their daily injections.

There's also this patient-to-parent relationship, and sometimes parents have been giving the injections to the child for many years and the child does not assume responsibility as they're getting older. So, there's also that degree of child autonomy that needs to be emphasized. And also, these devices are temperature-sensitive to storage, so if a child is on a school or a field trip, they may not be aware that if they leave their injection device outside and not refrigerated, that it can go bad and they may not be effective. There's also formulary changes and sometimes some kids prefer their older brands and when they are switched over to newer brands, they may not like it simply because maybe the pen is not as user-friendly as before. So there are certain nuances that may actually affect and dictate patients following through with their treatment.

There's also the responsibility of frequent visits for monitoring, at least every 6 to 12 months. Blood work to be monitored like IGF-1 and also

serial and bone x-rays that the parent and the patient needs to follow through with these visits with their providers.

CONCLUSION

Daily growth hormone has a proven record for efficacy and safety in growth hormone deficient adults and children. However, there may be multiple barriers to daily growth hormone therapy, particularly in the transition age. Nonadherence with daily growth hormone therapy can contribute to poor growth and possibly long-term bone and cardiovascular health. The need to address this nonadherence, several long-acting growth hormone preparations are now undertaken and being studied and the data indeed suggest that they hold promise of improving treatment and ultimately treatment outcomes for these patients.